

## Inorganic Arsenic Reference Exposure Levels

### 1. Summary

Acute, 8-hour and chronic reference exposure levels (RELs) were derived for inorganic arsenic including arsine. Inorganic arsenic causes a wide variety of toxic effects in humans and experimental animals including effects on development, the vascular system, the nervous system, blood, lung, and skin. The most sensitive acute effects were seen in mice (fetal development) whereas the most sensitive 8-hour and chronic effects were decreased intellectual function in children. The key values are summarized below.

#### 1.1 Inorganic Arsenic Acute REL

|                                 |  |
|---------------------------------|--|
| <i>Reference Exposure Level</i> | <b>0.2 µg As/m<sup>3</sup></b>   |
| <i>Critical effect(s)</i>       | Decreased fetal weight in mice   |
| <i>Hazard Index target(s)</i>   | Development (teratogenicity);<br>cardiovascular system; nervous system |

#### 1.2 Inorganic Arsenic 8-Hour REL

|                                      |   |
|--------------------------------------|---|
| <i>Reference Exposure Level</i>      | <b>0.015 µg/ As/m<sup>3</sup></b>   |
| <i>Oral Reference Exposure Level</i> | 0.0035 µg/kg bw-day   |
| <i>Critical effect(s)</i>            | Decreased intellectual function in 10 year<br>old children                            |
| <i>Hazard Index target(s)</i>        | Development (teratogenicity);<br>cardiovascular system; nervous system;<br>lung; skin |

#### 1.3 Inorganic Arsenic Chronic REL

|                                      |  |
|--------------------------------------|--|
| <i>Reference Exposure Level</i>      | <b>0.015 µg As/m<sup>3</sup></b>                           |
| <i>Oral Reference Exposure Level</i> | 0.0035 µg/kg bw-day  |
| <i>Critical effect(s)</i>            | Decreased intellectual function in 10 year<br>old children |
| <i>Hazard Index target(s)</i>        | Hematologic  |

## 2. Physical & Chemical Properties

**Table 2.1 Arsenic and Arsenic Species\***

| <b>Molecular formula</b>   | <b>Molecular weight</b> | <b>Percent As by weight</b> | <b>Synonyms</b>  | <b>CAS Registry Number</b> |
|--|-------------------------|-----------------------------|--|----------------------------|
| As   | 74.92                   | 100%                        | Arsenic black, metallic arsenic  | 7440-38-2                  |
| As <sub>2</sub> O <sub>3</sub><br>As <sub>4</sub> O <sub>6</sub> | 197.82<br>395.68        | 75.7%                       | Arsenious oxide, arsenic (III) trioxide, arsenic oxide, arsenous acid, arsenous acid anhydride, Crude Arsenic, White Arsenic | 1327-53-3                  |
| AsCl <sub>3</sub>  | 181.28                  | 41.3%                       | Arsenic butter, trichloroarsine, arsenious chloride  | 7784-34-1                  |
| As <sub>2</sub> O <sub>5</sub>                                   | 229.82                  | 65.2%                       | Arsenic pentoxide, arsenic anhydride, arsenic oxide, arsenic acid anhydride  | 1303-28-2                  |
| AsHNa <sub>2</sub> O <sub>4</sub>                                | 185.91                  | 40.3%                       | Arsenic acid disodium salt, disodium arsenate, sodium arsenate dibasic   | 7778-43-0                  |
| AsHNa <sub>2</sub> O <sub>3</sub>                                | 130.92                  | 57.2%                       | Arsenous acid disodium salt, arsenious acid sodium salt  | 7784-46-5                  |
| AsH <sub>3</sub>   | 77.94                   | 96.12                       | Arsine, arsane, arsenic hydride, arsenous hydride, hydrogen arsenide, arsenic trihydride                                     | 7784-42-1                  |
| As(OH) <sub>3</sub>  |                         |                             | Arsenous acid  | 13464-58-9                 |
| AsO(OH) <sub>3</sub>   | 141.93                  | 52.78                       | Arsenic acid, orthoarsenic acid  | 7778-39-4                  |
| As <sub>4</sub> S <sub>4</sub>                                   | 427.92                  | 70.03                       | Arsenic disulfide, realgar, red arsenic sulfide  |                            |
| CH <sub>3</sub> AsO(OH) <sub>2</sub>                             | 139.97                  | 53.51                       | Monomethylarsonic acid   | 124-58-3                   |
| CH <sub>3</sub> As(OH) <sub>2</sub>                              | 123.77                  | 60.41                       | Monomethylarsonous acid  | 25400-23-1                 |
| (CH <sub>3</sub> ) <sub>2</sub> AsO(OH)                          | 137.99                  | 54.28                       | Dimethylarsinic acid, cacodylic acid   | 75-60-5                    |
| (CH <sub>3</sub> ) <sub>2</sub> AsOH                             | 121.99                  | 61.40                       | Dimethylarsinous acid  | 55094-22-9                 |
| (CH <sub>3</sub> ) <sub>3</sub> AsO                              | 136.02                  | 55.06                       | Trimethylarsine oxide  | 4964-14-1                  |

\*Note: Methylated arsenic species occurring naturally and as metabolites (IARC, 2004)

**2.1 Arsenic (Metallic) (ATSDR, 2000)**

|                                     |  |
|-------------------------------------|--|
| <i>Description</i>                  | Yellow, black or gray solid                |
| <i>Molecular formula</i>            | see Table 2.1                              |
| <i>Molecular weight</i>             | see Table 2.1                              |
| <i>Specific gravity (water = 1)</i> | 5.778 g/cm <sup>3</sup> @ 25°C             |
| <i>Boiling point</i>                | 613°C (sublimes) at 760 mm Hg              |
| <i>Vapor pressure</i>               | 7.5 x 10 <sup>-3</sup> mmHg at 280 °C      |
| <i>Flashpoint</i>                   | not applicable                             |
| <i>Explosive limits</i>             | not applicable                             |
| <i>Solubility</i>                   | soluble in nitric acid, insoluble in water |
| <i>Odor threshold</i>               | not applicable                             |
| <i>Odor description</i>             | odorless                                   |
| <i>Metabolites</i>                  | dimethylarsinic acid, methylarsonic acid   |
| <i>Conversion factor</i>            | not applicable for As                      |

**2.2 Arsenic Trioxide (ATSDR, 2000)**

|                          |   |
|--------------------------|---|
| <i>Description</i>       | As <sub>2</sub> O <sub>3</sub> : White solid, glassy, amorphous lumps or crystal  |
| <i>Molecular formula</i> | See Table 2.1   |
| <i>Molecular weight</i>  | 197.84  |
| <i>Density</i>           | As <sub>2</sub> O <sub>3</sub> : 3.865 g/cm <sup>3</sup>                          |
| <i>Boiling point</i>     | As <sub>2</sub> O <sub>3</sub> : 460°C  |
| <i>Melting point</i>     | As <sub>2</sub> O <sub>3</sub> : 274°C  |
| <i>Solubility</i>        | Oxides: slightly soluble in water 17g/L, insoluble in alcohol, chloroform, ether. |
| <i>Metabolites</i>       | Dimethylarsinic acid, methylarsonic acid  |

**2.3 Arsine (U.S. EPA, 2006a)**

|                                     |   |
|-------------------------------------|---|
| <i>Description</i>                  | Colorless gas   |
| <i>Molecular formula</i>            | AsH <sub>3</sub>  |
| <i>Molecular weight</i>             | 77.93   |
| <i>Specific gravity (Water = 1)</i> | 1.689 @ 84.9°C  |
| <i>Boiling point</i>                | -62.55°C  |
| <i>Melting point</i>                | -117°C  |
| <i>Vapor pressure</i>               | Greater than 1 atm  |
| <i>Vapor density (Air = 1)</i>      | 2.695   |
| <i>Solubility</i>                   | soluble in chloroform and benzene, slightly soluble in water (20 mL/100 mL at 20 C), ethyl alcohol and in alkalis |
| <i>Odor threshold</i>               | 0.5 ppm   |
| <i>Odor description</i>             | garlic-like or fishy odor   |
| <i>Metabolites</i>                  | oxidation to arsenite, arsenate, other unidentified (Landrigan et al., 1982; Carter et al., 2003)                 |
| <i>Conversion factor</i>            | 1 ppm = 3.19 mg/m <sup>3</sup> @ 25°C   |

### 3. Occurrence and Major Uses

Arsenic is ubiquitous and is found in small amounts in soils and water throughout the world and also in foods, particularly seafood (NIOSH, 1975). Ore refining processes, including the smelting of copper and lead, are the major sources of release of arsenic dust and inorganic arsenic compounds. Arsenic trioxide is the form of inorganic arsenic most commonly produced. It is used as a raw material for the production of other inorganic arsenic compounds, alloys, and organic arsenic compounds (Grayson, 1978).

Pesticides have historically constituted the largest single use (50%) of arsenic compounds (HSDB, 1995). The major arsenic herbicides manufactured are monosodium methyl arsonate (MSMA), disodium methyl arsonate (DSMA), and dimethyl arsenic acid (cacodylic acid). Inorganic arsenic compounds are also used as herbicides (arsenite), insecticides (arsenic trioxide, calcium and other arsenates), or rodenticides (sulfides) (ACGIH, 1992). Arsenic trichloride, for example, is used mainly as a chemical intermediate in the production of insecticides, but has other applications in the ceramics and pharmaceutical industries (HSDB, 1995). Arsenic was used as a pesticide to treat tobacco; thus, cigarette smoke was another common source of exposure (U.S.EPA, 1984). The use of arsenic compounds in agriculture has reduced in recent years and U.S. EPA is considering ending their uses under the pesticide reregistration program (U.S. EPA, 2006b).

Arsenic-based wood preservatives have constituted the next largest use (40%) of arsenic compounds (HSDB, 1995). In December 2003 the U.S. EPA terminated all residential uses of wood preservatives containing arsenic limiting such products to restricted use by certified pesticide applicators (U.S. EPA, 2002).

The highly toxic trivalent arsenic compounds, such as arsenic trioxide, are typically introduced into the environment as a result of industrial processes including the smelting of metal ores. Pentavalent arsenic compounds are generally considered to be less toxic and are most frequently found naturally.

Processes such as smelting, galvanizing, soldering, and etching, that require the treatment of metal with strong acids, are possible sources of arsine gas. Acid treatment of metals contaminated with arsenic can result in the release of arsine gas. Arsine is used to provide arsenic as a dopant in the semiconductor industry. Combustion of fossil fuels may produce arsine gas.

### 4. Toxicokinetics

A knowledge of the metabolism of inorganic arsenic has long been thought to be essential to understanding the mode(s) of action of inorganic arsenic toxicity. Trivalent (+3) arsenic species (e.g., arsenite) have often exhibited greater acute toxicity than pentavalent (+5) species (e.g., arsenate). Since the metabolism of inorganic arsenic in mammalian species generally proceeds via alternate reductive and oxidative methylation steps to

mono- (MMA) and dimethyl (DMA) arsenic acids, it was believed that methylation represented detoxication of inorganic arsenic. However, recent evidence supports the idea that trivalent methylated species are in some cases more toxic than inorganic precursors and may play a key role in arsenic toxicity for selected endpoints. The metabolism of arsine (-3), while less studied, appears to progress similarly after its oxidation to arsenite (+3) and is in part the basis for including arsine in the RELs for inorganic arsenic.

Several comprehensive reviews of the absorption, distribution, metabolism and elimination of arsenic have been published (Vahter, 1983; Thompson, 1993; ATSDR, 2000; NRC, 2001). Most information on the toxicokinetics of arsenic derives from oral exposure studies. The kinetics of arsenic varies depending on the chemical form of arsenic and on the animal species. The following discussion is limited to the oxidized forms found in water and air and forms that are ingested via the aquatic food chain. These include the inorganic, soluble forms of arsenite ( $\text{As}^{\text{III}}$ ) and arsenate ( $\text{As}^{\text{V}}$ ), as well as the organic methyl arsonate (MMA), dimethylarsinic acid (DMA), trimethylarsine (TMA), and or arsenobetaine (in fish).

## 4.1 Inorganic Arsenic Oxides

### 4.1.1 Absorption and Distribution

Owen (1990) reported inhalation absorption of 32 percent (range 30 to 34 %) from arsenic containing aerosols, however it is uncertain if this figure included the gastrointestinal absorption of arsenic particles from the upper respiratory tract. The International Commission on Radiological Protection Human Respiratory Tract Model (ICRP, 1994) gives total deposition fractions for 10 yr old children inhaling 1  $\mu\text{m}$  activity median thermodynamic diameter particles at 0.31 to 2.03  $\text{m}^3/\text{hr}$  of 0.42 to 0.58. There are relatively few data on the kinetics of airborne arsenic excretion. Mann et al. (1996a) modeled inhalation exposures based on the occupational data of Vahter et al. (1986) and Offergelt et al. (1992). For simulated occupational exposures of 10  $\mu\text{g}/\text{m}^3$  of arsenic aerosol of MMAD of 5.0  $\mu\text{m}$ , GSD of 2.1, 1.2 L tidal volume and a breathing rate of 16 /min, urinary excretion increased over the work week's exposure from 7 to 25  $\mu\text{g}$  As/g creatinine. Model predictions of arsenic metabolites (Asi, MMA, DMA) in postshift urine generally fell within the range of observations for 18 workers in the exposure range of 10-1000  $\mu\text{g}$  As/ $\text{m}^3$ . After daily inhalation exposure of 100  $\mu\text{g}$  As (III)/ $\text{m}^3$  for three weeks, the model predictions for urinary metabolite distribution closely matched observed values (predicted/observed means: Asi, 1.05; MMA, 1.0; DMA, 1.0). From the model, Mann et al. (1996b) derived a fitted lung absorption first order rate constant for arsenic trioxide dust of 0.01/ $\text{cm}^2\text{-hr}$ .

In general, investigations that have monitored arsenic excretion of experimental animals following parenteral administration have demonstrated that only a small fraction of the administered arsenic is excreted in the feces. Thus, to estimate the amount of inorganic arsenic absorbed following oral administration, most kinetic and metabolic studies have

monitored the urine. Soluble compounds of inorganic arsenic, whether in the trivalent or pentavalent form, are readily absorbed (80-90 percent) in most animal species following oral administration (Charbonneau et al., 1978; Vahter, 1981; Hughes et al., 1994; Freeman et al., 1995). However, only about 40-50 percent absorption has been reported in hamsters (Yamauchi and Yamamura, 1985; Marafante and Vahter, 1987). Absorption of orally administered inorganic arsenic in humans has been shown to range between 54-80 percent (Tam et al., 1979; Buchet et al., 1981b; a; Kurttio et al., 1998).

Inorganic arsenic compounds are poorly absorbed through the skin (Ca.1-5%); the trivalent is more rapidly absorbed than the pentavalent (Wester et al., 1993; Wester et al., 2004).

Organic forms of arsenic are also extensively absorbed from the gastrointestinal tract. Experimental studies examining the absorption of MMA, DMA, TMA and arsenobetaine in humans have demonstrated 75-92 percent absorption. At low-level exposures, excretion of arsenic and its metabolites seems to balance absorption of inorganic arsenic. With increasing arsenic intake, there is suggestive evidence that methylation appears less complete. Studies, which examine the effect of dose on excretion patterns, have been conducted in mice and humans (Buchet et al., 1981b; a; Vahter, 1981). As the dose of inorganic arsenic increases, the percent of arsenic excreted as DMA decreases, accompanied by an increased excretion in the percent as inorganic arsenic. The percent excreted as MMA remains virtually unchanged. *In vitro* metabolism studies on the methylation of inorganic arsenic have demonstrated that the liver is the site of methylating activity and that S-adenosylmethionine and reduced glutathione are required as methyl donors (Buchet and Lauwerys, 1985; 1987).

While absorption from the gastrointestinal tract is the most important route of exposure for waterborne arsenic, some potential for dermal absorption has been reported. Rahman et al. (1994) conducted *in vitro* studies with sodium [<sup>74</sup>As] arsenate and clipped full-thickness mouse skin in a flow-through system. Doses of 5, 50, 500, or 5000 ng were applied to 0.64 cm<sup>2</sup> of skin as a solid, in aqueous vehicle, or in soil. Absorption of sodium arsenate increased linearly with applied dose from all vehicles. The maximum absorption of 62 percent of applied dose was obtained with the aqueous vehicle and the least (0.3 percent) with soil. Wester et al. (1993) evaluated the percutaneous absorption of [<sup>73</sup>As] arsenate from soil or water *in vivo* in Rhesus monkeys and *in vitro* in human cadaver skin. Water solutions of [<sup>73</sup>As] arsenate at low (0.024 ng/cm<sup>2</sup>) or high (2.1 µg/cm<sup>2</sup>) surface concentrations were compared. With topical administration for 24 hr, *in vivo* absorption in the Rhesus monkey was 6.4 ± 3.9 (SD) percent from the low dose and 2.0 ± 1.2 (SD) percent from the high dose. *In vitro* percutaneous absorption of the low dose from water in human skin was 0.93 ± 1.1 percent in receptor fluid and 0.98 ± 0.96 percent in the washed skin; the total was about 1.9 percent. Absorption from soil (0.4 ng/cm<sup>2</sup>) was less, at 6.4 percent in the monkey *in vivo* and 0.8 percent in human skin *in vitro*.

The retention and distribution patterns of arsenic are in part determined by its chemical properties. Arsenite (As<sup>III</sup>) reacts and binds to sulfhydryl groups while arsenate (As<sup>V</sup>) has

chemical properties similar to those of phosphate.  $\text{As}^{\text{V}}$  also has affinity for sulfhydryl groups; however, its affinity is approximately 10-fold less than  $\text{As}^{\text{III}}$  (Jacobson-Kram and Montalbano, 1985). The distribution and retention patterns of  $\text{As}^{\text{III}}$  and  $\text{As}^{\text{V}}$  are also affected by species, dose level, methylation capacity, valence form, and route of administration.

Vahter et al. (1984) studied tissue distribution and retention of  $^{74}\text{As}$ -DMA in mice and rats. About 80 percent of an oral dose of 0.4 mg As/kg was absorbed from the gastrointestinal tract. In mice >99 percent of the dose was excreted within 3 d compared to only 50 percent in rats, due largely to accumulation in blood. Tissue distribution in mice showed the highest initial (0.5-6 hr) concentrations in kidneys, lungs, intestinal mucosa, stomach, and testes. Tissues with the longest retention times were lungs, thyroid, intestinal walls, and lens.

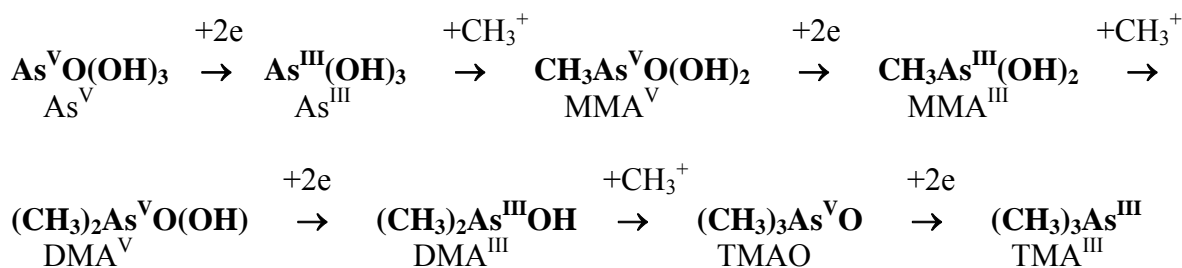
The effect of dose on arsenate disposition was evaluated in adult female B6C3F<sub>1</sub> mice dosed orally with 0.5 to 5000  $\mu\text{g/kg}$  [ $^{73}\text{As}$ ]-arsenate in water (Hughes et al., 1994). Urine was collected at several time points over a 48-hr period, and feces at 24 and 48 hr post-exposure. The recovery of As-derived radioactivity in excreta and tissues ranged from 83.1 to 89.3 percent of dose. As-derived radioactivity was detected in several tissues (urinary bladder, gall bladder, kidney, liver, lung) although the sum for each exposure level was very low (<0.5 percent of dose). The principal depot was the liver, followed by the kidneys. As the dose of arsenate increased there was a significant increase in the accumulation of radioactivity in the urinary bladder, kidney, liver, and lungs. The greatest concentration of As radioactivity was in the urinary bladder.

#### 4.1.2 Metabolism

Most studies of arsenic metabolism have involved administration of inorganic arsenic (Asi) as arsenate ( $\text{As}^{\text{V}}$ ) or arsenite ( $\text{As}^{\text{III}}$ ) to an experimental animal or a human, and detection of Asi and the methylated metabolites methylarsonic acid ( $\text{MMA}^{\text{V}}$ ) and dimethylarsinic acid ( $\text{DMA}^{\text{V}}$ ) in urine, feces, and tissues.

Thompson (1993) conducted an extensive review and analysis of the mammalian metabolic data on arsenic. The metabolism of arsenate can be viewed as a cascade of reductive and oxidative methylation steps leading successively to  $\text{As}^{\text{III}}$ ,  $\text{MMA}^{\text{V}}$ ,  $\text{MMA}^{\text{III}}$ ,  $\text{DMA}^{\text{V}}$ ,  $\text{DMA}^{\text{III}}$ ,  $\text{TMAO}^{\text{V}}$ , and TMA as outlined in Scheme 1. Recently Hayakawa et al. (2005) proposed a new metabolic pathway for arsenite, which does not involve oxidative methylation but rather is mediated by As-glutathione complexes, S-adenosylmethionine (SAM) and human arsenic methyltransferase Cyt19. In this pathway arsenic triglutathione ( $\text{As}(\text{SG})_3$ ) is converted to monomethyl-(MADG) and dimethyl-(DMAG) conjugates which are hydrolyzed to  $\text{MMA}^{\text{III}}$  and  $\text{DMA}^{\text{III}}$ , respectively. Thus pentavalent methylated metabolites might arise via oxidation of their trivalent forms rather than the reverse as shown in Scheme 1.

**Scheme 1. Biomethylation of Arsenic Involving Alternate Reduction of Pentavalent Arsenic to Trivalent Arsenic Followed by Oxidative Addition of a Methyl Group (after Jiang et al. (2003))**



MMA<sup>III</sup> and DMA<sup>III</sup> have only recently been detected as stable urinary metabolites in human subjects (Aposhian et al., 2000a; Aposhian et al., 2000b; Le et al., 2000a; Le et al., 2000b), and trimethylarsine oxide (TMAO) and trimethylarsine (TMA) are rarely seen and are very minor metabolites in most mammals if found at all. Few data are available on the tissue concentrations of trivalent methylated As species (Kitchin, 2001). Gregus et al. (2000) found that in bile duct-cannulated rats, As<sup>III</sup> and its metabolites were preferentially excreted into bile (22 percent) versus eight percent into urine in two hr. Arsenite appeared in bile rapidly and constituted the large majority in the first 20 min. Thereafter As<sup>III</sup> declined and MMA<sup>III</sup> output gradually increased. From 40 min after i.v. As<sup>III</sup> administration, MMA<sup>III</sup> was the dominant form of biliary arsenic. Within two hr 9.2 percent of the dose was excreted in the bile as MMA<sup>III</sup>. Injection of arsenate produced a mixture of As<sup>V</sup>, As<sup>III</sup> and MMA<sup>III</sup> in the bile. Curiously, rats injected with MMA<sup>V</sup> did not excrete MMA<sup>III</sup>.

The metabolism results of Styblo et al. (1995) in rat liver cytosol *in vitro* seem to support the overall metabolic scheme noted above; MMA<sup>III</sup> and MMA<sup>III</sup>-diglutathione complex are more rapidly methylated to the dimethyl forms than MMA<sup>V</sup>. Thompson also suggests that the data support the presence of two inhibitory loops: (1) competitive inhibition by MMA<sup>III</sup> of the As<sup>III</sup> → MMA<sup>V</sup> step catalyzed by MMTase; and (2) possibly noncompetitive inhibition by As<sup>III</sup> of the MMA<sup>III</sup> → DMA<sup>V</sup> step catalyzed by DMTase.

Styblo et al. (1996) observed 50 μM arsenite inhibition of DMA<sup>V</sup> production in rat liver cytosol *in vitro*. Healy et al. (1998) studied the activity of MMTase in tissues of mice. The activity was determined with sodium arsenite and S-[methyl-<sup>3</sup>H]-adenosyl-L-methionine by measuring the formation of [methyl-<sup>3</sup>H] monomethylarsonate. The mean MMTase activities (units/mg ± SEM) measured in cytosol of mouse tissues were: liver, 0.40 ± 0.06; testis, 1.45 ± 0.08; kidney, 0.70 ± 0.06; and lung, 0.22 ± 0.01. When mice were given arsenate in drinking water for 32 or 92 days at 25 or 2500 μg As/L, the MMTase activities were not significantly increased compared to controls. MMTases and DMTases have been partially purified from the livers of rabbits (Zakharyan et al., 1995), Rhesus monkeys (Zakharyan et al., 1996) and hamsters (Wildfang et al., 1998). All of the enzyme preparations exhibited Michaelis-Menten enzyme kinetics with Km values ranging from 8x10<sup>-4</sup> M for hamster DMTase to 1.8x10<sup>-6</sup> M for hamster MMTase. Vmax values ranged from 0.007 pmol/mg protein/hr for hamster DMTase to 39.6 pmol/mg



protein/hr for rabbit MMTase. Comparative studies have shown several species to be deficient in methyltransferase activities, notably New World monkeys, marmosets, tamarin, squirrel, chimpanzee, and guinea pig (Vahter et al., 1995b; Aposhian, 1997). While comparisons with human arsenic methyl transferase are limited by lack of a purified human enzyme, based on excretion profiles of urinary metabolites the rabbit and hamster appear most pharmacokinetically similar to humans than the other species studied. Walton et al. (2003) compared the methylation of arsenite by rat and human primary hepatocytes *in vitro* (control values in their Tables 1 and 2). For the rat the methylation rate after a 3 hr incubation with 0.1  $\mu\text{M}$  arsenite was  $99.3 \pm 1.87$  pmol  $\text{CH}_3/\text{hr}/10^6$  cells (mean  $\pm$  SD,  $N=4$ ). The human hepatocytes similarly exposed for 24 hr had a methylation rate of  $1.68 \pm 0.24$  pmol  $\text{CH}_3/\text{hr}/10^6$  cells, over a 50-fold difference in apparent methylation rate.

While the reduction of arsenate and  $\text{MMA}^{\text{V}}$  can be accomplished nonenzymatically *in vitro*, and arsenate reduction by glutathione occurs in mammalian blood *in vivo* (Vahter and Envall, 1983; Winski and Carter, 1995), these reductive steps are most likely enzymatically mediated *in vivo*. An arsenate reductase has been partially purified from human liver and described (Radabaugh and Aposhian, 2000). The approximate mass of the enzyme was 72,000. It was specific for arsenite (i.e., did not reduce  $[^{14}\text{C}] \text{MMA}^{\text{V}}$ ) and exhibited substrate saturation at about 300  $\mu\text{M}$ . The human arsenate reductase requires a thiol and a heat-stable cofactor and is apparently distinct from those isolated from bacteria (Ji and Silver, 1992; Gladysheva et al., 1994; Krafft and Macy, 1998).

Monomethyl arsonate ( $\text{MMA}^{\text{V}}$ ) reductases have been isolated and described for rabbit (Zakharyan and Aposhian, 1999) and hamster (Sampayo-Reyes et al., 2000). In the latter study the distribution of  $\text{MMA}^{\text{V}}$  reductase activity was 91.4 nmol  $\text{MMA}^{\text{III}}/\text{mg}$  protein/hr in brain and 61.8 nmol  $\text{MMA}^{\text{III}}/\text{mg}$  protein/hr in bladder. Skin, kidney and testis all had less than 15 nmol/mg/hr. Spleen, liver, lung, and heart were all between 15 and 62 nmol/mg/hr. The high activity of  $\text{MMA}^{\text{V}}$  reductase in brain is curious and may help explain some of the neurotoxic effects of arsenic. Due to relatively low affinity of the  $\text{MMA}^{\text{V}}$  reductase ( $K_{\text{M}} = 2.2 \times 10^{-3}$  M) compared to the methyl transferases ( $K_{\text{M}} = 5\text{-}9 \times 10^{-6}$  M), the  $\text{MMA}^{\text{V}}$  reduction is thought to be the rate-limiting step in arsenic metabolism (Zakharyan and Aposhian, 1999). The partially purified human liver  $\text{MMA}^{\text{V}}$  reductase has been shown to be identical with human glutathione S-transferase Omega class hGSTO 1-1 (Zakharyan et al., 2001).

DMA is the main metabolite found in the tissues and urine of most experimental animals administered inorganic arsenic. Humans are also somewhat unique in that MMA has been found to be an important metabolite of inorganic arsenic in addition to DMA. Studies conducted on human volunteers given a single oral dose of inorganic arsenic demonstrated that within 4-7 days, 46-62 percent of the dose was excreted in the urine (Tam et al., 1979; Pomroy et al., 1980; Buchet et al., 1981b; a). Approximately 75 percent of the excreted arsenic is methylated, about one-third as MMA and two-thirds as DMA.

The possibility of genetic polymorphism in arsenic metabolism has been suggested by Vahter et al. (1995a), who studied native Andean women in northwestern Argentina who were exposed to a wide range of As concentrations in drinking water (2.5 to 200 µg As/L). The women exposed to the highest As concentration in water exhibited surprisingly low levels of MMA in their urine (2.3 percent of metabolites). The percentage of arsenic urinary metabolites as MMA in typical human urine ranges from 12 to 20. Chiou et al. (1997a) studied the relationships among arsenic methylation capacity, body retention, and genetic polymorphisms of glutathione-S-transferase (GST) M1 and T1 in 115 human subjects. Percentages of As species in urine (mean ± SE) were: Asi, 11.8 ± 1.0; MMA, 26.9 ± 1.2; and DMA, 61.3 ± 1.4. Genetic polymorphisms of GST M1 and T1 were significantly associated with As methylation. Subjects with the null genotype of GST M1 had an increased percentage of Asi in urine, while those with the null genotype GST T1 had elevated DMA in their urine samples.

Marnell et al. (2003) reported six polymorphisms in the MMA<sup>V</sup> reductase hGSTO1 gene in DNA isolated from peripheral blood of 75 Mexican subjects. Two subjects with the same polymorphism showed 5 to 10 fold higher concentrations (µg/g creatinine) of Asi in their urine than other subjects.

Yu et al. (2003) screened DNA of 22 subjects of European ancestry (EA) and 24 of indigenous American ancestry (IA) for polymorphisms in arsenate reductase and MMA<sup>V</sup> reductase genes. For the arsenate reductase gene (hPNP) 48 polymorphic sites were identified while 33 were found in the MMA<sup>V</sup> reductase gene (hGSTO1-1). For the EA individuals the MMA<sup>V</sup> reductase gene showed greater polymorphism than the arsenate reductase gene whereas the reverse was seen in the IA individuals. In the latter group only one polymorphism had a frequency of > 10%. Meza et al. (2005) screened 135 As-exposed subjects from Sonora, Mexico for polymorphisms in arsenic metabolism genes: arsenate reductase (hPNP); MMA<sup>V</sup> reductase (hGSTO); and arsenic 3 methyltransferase (CYT19). The subjects were exposed to drinking water with 5.5 to 43.3 ppb arsenic. The screening was based on urinary DMA<sup>V</sup>/MMA<sup>V</sup> (D/M) ratios. The analysis revealed that all of the variation was due to a very strong association between CYT19 and D/M in children only (7-11 yr). With children removed no significant association was seen in adults (18-79 yr). This developmentally regulated association between CYT19 and arsenic metabolism raises questions about the adequacy of arsenic risk assessment for children.

#### 4.1.3 Excretion

Several authors have studied the kinetics of As excretion in humans. Tam et al. (1979) administered <sup>74</sup>As arsenic acid (0.01 µg, ca. 6 µCi) to six adult males (age: 28-60; body weight: 64-84 kg) following an overnight fast. The urine was analyzed at 24 hr intervals for five days following As administration. In the first 24 hr period Asi excretion exceeded that of the methylated metabolites but thereafter the usual DMA > MMA > Asi pattern persisted, with DMA increasing in percentage of cumulative excretion at the later time points. A follow up study (Pomroy et al., 1980) followed <sup>74</sup>As excretion for periods

up to 103 days using a whole body counter, with measurement of excreta for the first seven days. Their results indicate that the excretion data were best represented by a three-component exponential function. The coefficients for the pooled data accounted for 65.7 percent of excretion with a half-life of 2.09 days, 30.4 percent with a half-life of 9.5 days, and 3.7 percent with a half-life of 38.4 days. A four-exponent function showed a better fit to one of the six subjects (half-lives: 0.017, 1.42, 7.70 and 44.1 days).

#### **4.1.4 PBPK Models**

Physiologically-based pharmacokinetic (PBPK) models employ data from various sources to mathematically simulate the uptake, distribution, metabolism and excretion of toxic chemicals in species of interest. Such models are used in risk assessment to estimate target tissue doses and to facilitate route-to-route and interspecies extrapolations. By contrast, pharmacodynamic (PD) models simulate biological responses to chemical exposures. A number of PBPK models for arsenic disposition and metabolism have been developed for experimental animals and humans (Mann et al., 1994; Menzel et al., 1994; Mann et al., 1996a; 1996b; Yu, 1999; Gentry et al., 2004). Although these models are based on somewhat different principles, they all seem to do a fair job in predicting the overall disposition of arsenic in animals and man. However, while the models often incorporate the latest ideas on the metabolism of inorganic arsenic with respect to oxidation state, methylated metabolites, and enzyme inhibition, due to limitations in our understanding of the modes of action of arsenic toxicity, they have yet to include representations of biological responses or pharmacodynamic (PD) capabilities, such as dosimetry linked alterations of DNA methylation, cell signaling pathways, DNA repair inhibition or generation of reactive oxygen species.

As an example of the complexity of arsenic action, Gentry et al. (2004) observed that pharmacodynamic changes occurred in mice without changes in PBPK predicted arsenic tissue dosimetry. These authors used the PBPK model of Mann et al. (1996a,b) extended to mice to evaluate possible dosimetry differences between mouse a strain susceptible to arsenic induced tumors (C57Bl/6J) and those that lacked susceptibility (e.g., Swiss CD-1, Swiss CD: NIH(S), C57Bl/6p53 (+/-)). The model was parameterized using published acute mouse data for arsenate, arsenite, MMA and DMA and validated with acute exposure data from the C57Black mouse strain. Model predictions for acute exposure were then compared with data from acute (24 hr) and chronic exposures (26 weeks). No differences were seen in the volume of distribution or tissue-plasma concentration ratios between acute and chronic exposures. Comparison of metabolite profiles in blood, liver and urine also showed little difference between acute and chronic exposures. Model predictions compared well with observed values. The authors concluded "... that pharmacokinetic factors do not provide an explanation for the difference in outcomes across the various mouse bioassays." This conclusion may be overly broad since all the metabolites of arsenic and its metabolic pathways were not included in the PBPK modeling.

## 4.2 Arsine

Although most studies of arsenic metabolism have centered on arsenate and arsenite, other forms of arsenic are also metabolized in humans. Apostoli et al. (1997) reported on the metabolism of arsine gas ( $\text{As}^{-\text{III}}\text{H}_3$ ) in an occupationally exposed worker. Arsenic species were analyzed in urine over a five-day post-exposure period by liquid chromatography and inductively coupled plasma mass spectroscopy. The As species most excreted were MMA, DMA,  $\text{As}^{\text{III}}$ , arsenobetaine (AsB), and to a lesser extent  $\text{As}^{\text{V}}$ . The data indicate a capability to oxidize  $\text{As}^{-\text{III}}$  to  $\text{As}^{\text{V}}$  species probably via arsenite  $\text{As}(\text{OH})_3$ . Arsenobetaine, an important form of arsenic in food, does not undergo subsequent biotransformation and is excreted via the urine. Curiously, arsenobetaine does not appear to be a metabolite of arsine in rats exposed for 1 hour to 4 to 80  $\text{mg}/\text{m}^3$  arsine (Buchet et al., 1998). The apparent similarity of the metabolism of arsine and arsenite is important and supports the use of the inorganic arsenic RELs for arsine.

Carter et al. (2003) have reviewed the metabolism of arsenic oxides, gallium arsenide and arsine. These authors describe three reactions that appear to occur in aqueous solutions of arsine ( $-\text{III}$ ): (1) the formation of elemental  $\text{As}^0$  and hydrogen; (2) reaction of  $\text{AsH}_3$  with oxidized thiols to form diarsine  $\text{AsH}_2\text{-AsH}_2$  (proposed) and reduced thiol  $\text{RSH}$ ; and (3) possible reaction between arsine and oxygen species, producing arsine hydroperoxide  $\text{H}_2\text{AsOOH}$  (Hatlelid et al., 1995; 1996). Relatively few studies of arsine metabolism have been conducted in experimental animals. In vitro studies indicate that arsine was rapidly distributed to red blood cells. In plasma arsine appeared to decompose over a few hours. Arsine apparently undergoes rapid oxidative metabolism although the intermediary metabolites have not been identified and apparently are not identical with those shown above for arsenite metabolism (Scheme 1) (Carter et al., 2003). A hypothetical scheme based on the same alternate application of oxidative methylation and reduction steps might look as follows with double arrows indicating four electron oxidation steps and single arrows two electron reduction steps:



**Arsine**

**TMAO**

According to this scheme the intermediary metabolites would include methylated arsine and arsine oxide species. Alternatively nonmethylative oxidation of arsine could lead to arsenite and arsenate via hydroxylated arsine species. Other metabolites possibly based on the oxidation of elemental As or arising via the postulated arsine hydroperoxide are also possible.

## 5. Acute Toxicity of Arsenic and Arsenic Compounds

### 5.1 Acute Toxicity to Adult Humans

The relative acute toxicity of arsenic compounds decreases as follows: arsine (-III) > organo-arsine derivatives > arsenites (III) > arsenoxides (III) > arsenates (V) > pentavalent organic compounds (V) > arsonium metals (I) > metallic arsenic (0), where the Roman numeral indicates the oxidation state (HSDB, 1995).

Acute inhalation exposure may result in severe irritation of the mucous membranes of the upper and lower respiratory tract with symptoms of cough, dyspnea, and chest pain (Friberg et al., 1986). These may be followed by garlicky breath and gastrointestinal symptoms including vomiting and diarrhea (HSDB, 1995). Signs of acute poisoning are dermatitis, nasal mucosal irritation, laryngitis, mild bronchitis, and conjunctivitis (Friberg et al., 1986). The acute toxic symptoms of trivalent arsenic poisoning are due to severe inflammation of the mucous membranes and increased permeability of the capillaries (HSDB, 1995). Ingestion of 2 grams of  $\text{As}_2\text{O}_3$  was fatal to an adult male (Levin-Scherz et al., 1987).

### 5.2 Acute Toxicity to Infants and Children

Relatively little data are available on acute toxicity of arsenic compounds to children. Childhood poisonings due to arsenic have been reported in the medical literature, often with little dosimetry. Campbell & Oates (1992) surveyed 200 child poisonings and found of the four deaths reported one was due to arsenic-containing weed killer (probably cacodylic acid). Alternatively, the use of arsenic trioxide in cancer chemotherapy seems well tolerated. George *et al.* (2004) reported the treatment of 11 children with acute promyelocytic leukemia with i.v. 0.15 mg  $\text{As}_2\text{O}_3$ /kg-d (8 treatment cycles over a period of 12 months). The toxic effects noted, including leukocytosis and skin hyperpigmentation, were considered minimal. Relapse-free survival was 81%.

### 5.3 Acute Toxicity to Experimental Animals

#### 5.3.1 Inhalation Exposure

The lethal concentration low ( $\text{LC}_{\text{Lo}}$ ) for  $\text{AsCl}_3$  in the cat for a 20-minute inhalation exposure is 100 ppm (740 mg/m<sup>3</sup>) (Flury, 1921). In the mouse, the  $\text{LC}_{\text{Lo}}$  of  $\text{AsCl}_3$  for a 10-minute exposure is 338 ppm (2500 mg/m<sup>3</sup>) (Flury, 1931).

A single intratracheal instillation of 17 mg  $\text{As}_2\text{O}_3$ /kg in rats resulted in multifocal interstitial pneumonia and focal proliferative bronchiolitis and alveolitis observed at necropsy 14 days post-exposure (Webb et al., 1986). The authors suggest that  $\text{As}_2\text{O}_3$  induced an acute fibrogenic response.

#### 5.3.2 Immunotoxicity

Changes in host resistance from inhalation exposure to  $\text{As}_2\text{O}_3$  aerosol were examined in female CD1 mice using a streptococcus infectivity model and an assay for pulmonary

bactericidal activity (Aranyi et al., 1981; Aranyi et al., 1985). Mice (100-200/group) were exposed to As<sub>2</sub>O<sub>3</sub> aerosol (or filtered air) for 3 hours/day, 5 days/week, for 1, 5 or 20 days. Aerosol exposed and control mice were then combined before challenge with *Streptococcus zoopidemicus* aerosol (4-8 replicate exposures). Statistically significant increases in mortality ( $P < 0.05$ ) were observed in mice exposed: (1) once to 271, 496, and 940  $\mu\text{g As/m}^3$ ; (2) 5 times to 519  $\mu\text{g As/m}^3$ ; and (3) 20 times to 505  $\mu\text{g As/m}^3$ . Multiple exposures at a given exposure level did not correlate with increased mortality, suggesting an adaptation mechanism. Single exposures did, however, show a dose-response for increased mortality with increasing level of arsenic exposure. Bactericidal activity was evaluated by measuring the ratio of viable bacteria count to radioactive count in the lung 3 hours after infection with <sup>35</sup>S-labeled *Klebsiella pneumoniae*. A single exposure to 271, 496, and 940  $\mu\text{g As/m}^3$ , but not 123  $\mu\text{g As/m}^3$ , resulted in significantly decreased bactericidal activity. Five exposures to 519  $\mu\text{g As/m}^3$  and twenty exposures to both 245 and 505  $\mu\text{g As/m}^3$  resulted in decreased bactericidal activity. The studies indicate a NOAEL for immunotoxicity of 123  $\mu\text{g As/m}^3$ . This study provides a partial mode of action of arsenic-induced increase in mortality due to experimental lung infections with the mouse pathogen *S.zoopidemicus*. The second bactericidal assay with radiolabelled *K.pneumoniae* provides a plausible explanation, namely that arsenic exposure above 123  $\mu\text{g/m}^3$  inhibits normal immune bactericidal response in the lung.

### 5.3.3 Organ and Enzyme Effects

Among the other adverse effects of inorganic arsenic noted in experimental animals, the most interesting and relevant to the 8-hour and chronic RELs are those on the brain and nervous system. These include changes in brain histology and conditioned reflexes, changes in locomotor activity, and decreased acetyl cholinesterase, GAD, and GABA levels in the hypothalamus, brain stem and cerebellum. Arsenic induced alterations of brain structure and function are consistent with the more subtle neuro-developmental effects seen in children exposed to inorganic arsenic at lower environmental levels.

## 5.4 Developmental and Reproductive Toxicity

Arsenic is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a developmental toxicant. The oxidation state of arsenic determines the teratogenic potential of its inorganic compounds; trivalent (III) arsenic compounds possess greater teratogenic potential than pentavalent (V) compounds. In hamsters, a single maternal intravenous injection of 20 mg/kg sodium arsenate (V) (AsHNa<sub>2</sub>O<sub>4</sub>) on gestation day 8 was lethal to 44% of all embryos (Willhite and Ferm, 1984). A smaller dose (10 mg/kg) of sodium arsenite (III) (AsHNaO<sub>2</sub>) administered in the same manner resulted in 90% embryonic lethality.

Fetal malformations, including exencephaly, resulted from an intravenous injection of AsH<sub>3</sub>Na<sub>2</sub>O<sub>4</sub> (V) into pregnant hamsters on gestation day eight (Ferm and Carpenter, 1968). The reproductive NOAEL in this experiment was 5 mg/kg. A significant reduction in fetal body weight, but no malformations were observed following a maternal

dose of 5 mg/kg  $\text{AsH}_2\text{NaO}_3$  (III) by the same route on gestation day eleven or twelve (Harrison and Hood, 1981).

A significant increase in pre-implantation mortality followed exposure of pregnant rats to aerosolized  $\text{As}_2\text{O}_3$  at 1 mg/m<sup>3</sup> for 5 months; no maternal toxicity was observed (Kamkin, 1982). At the LOAEL, 0.3 mg/m<sup>3</sup>, slightly elevated pre-implantation lethality was observed. The validity of this report cannot be evaluated, however, because key experimental details were not reported.

A significant decrease in spermatozoa motility was observed in male rats following continuous exposure to  $\text{As}_2\text{O}_3$  at a concentration of 40 mg/m<sup>3</sup> for 48 hours (Kamil'dzhanov, 1982). Intravenous injection of radioactive arsenate (V) or arsenite (III) in several rodent species, including mice and hamsters, resulted in accumulation of arsenic in the lumen of the epididymal duct, which suggests that long term exposure of sperm may occur *in vivo* following acute exposure to As (Danielsson et al., 1984).

Nagymajtenyi et al., (1985) exposed pregnant CFLP mice (8-11 females/group) to  $\text{As}_2\text{O}_3$  aerosol for 4 hours/day on gestational days 9-12 at concentrations of 0, 0.26, 2.9, or 28.5 mg  $\text{As}_2\text{O}_3$ /m<sup>3</sup> (~0.2, 2.2, and 21.6 mg As/m<sup>3</sup>). The aerosol was generated by spraying an aqueous solution of  $\text{As}_2\text{O}_3$ . On the 18<sup>th</sup> day of gestation the mice were sacrificed and the fetuses removed. The numbers of live and dead fetuses were recorded, weighed, and examined microscopically. Fifty fetuses were stained with Alizarin red-S for skeletal examination. Chromosome preparations were made from livers of 10 fetuses per exposure group. Twenty mitoses in each fetus (200/group) were scored for chromosomal damage and 10 percent of these were karyotyped. The data were analyzed with either Fisher's exact test or in the case of fetal weights with the Dunnett multiple comparison t-test.

A statistically significant decrease in fetal weight was observed in all of the dose groups ( $P < 0.05$ ), with a 3, 9, and 29% reduction in average fetal weight with increasing dose (Table 6.4.1). Significantly delayed bone maturation (ossification defects) was observed only in the highest dose group (sternum 14/50; limbs 32/50, both  $p < 0.05$ ). However, an apparent positive dose-related trend in the number of fetuses with skeletal malformations was observed (2 [control], 3, 7, 31, respectively). A similar dose-related trend in chromosome aberrations in liver cells was also observed in the number of cells with damage (6[control], 10, 13, 24), chromatid gaps, chromatid breaks, chromosome fragments, and chromosome breaks (5[control], 10, 13, 27). Only the number of damaged cells and chromosome breaks at the high dose were significantly different from the control ( $p < 0.05$ ).

**Table 6.4.1 Data from Table 1 of Nagymajtényi et al. (1985).**

| As <sub>2</sub> O <sub>3</sub><br>(mg/m <sup>3</sup> ) | <u>Number of<br/>litters</u> | Living fetuses<br>per mother | Number of<br>fetuses<br>examined | % dead<br>fetuses | Average fetal<br>weight<br>(grams) |
|--|------------------------------|------------------------------|----------------------------------|-------------------|------------------------------------|
| 28.5±0.3   | 11                           | 9.6                          | 100                              | 29                | 0.981±0.04*                        |
| 2.9±0.04   | 8                            | 12.8.                        | 100                              | 13                | 1.146±0.03*                        |
| 0.26±0.01  | 8                            | 12.5                         | 100                              | 12                | 1.225±0.03*                        |
| 0  | 8                            | 12.5                         | 100                              | 8                 | 1.272±0.02                         |

\* Significantly different from control (p<0.05)

This study demonstrates that inhalation exposure to inorganic arsenic is markedly fetotoxic. Arsenic concentrations of 28.5 mg/m<sup>3</sup> caused a reduction in the number of live fetuses, in fetal weight, and an increase in fetuses with delayed osteogenesis.

Rats exposed to 1 µg As<sub>2</sub>O<sub>3</sub>/m<sup>3</sup> (0.76 µg As/m<sup>3</sup>) for 5 months showed increased preimplantation mortality and delayed ossification in fetuses (Kamkin, 1982). Experimental detail was not presented, thus limiting the usefulness of this study.

A significant decrease in spermatozoa motility was observed in male rats following continuous exposure to 32.4 mg As<sub>2</sub>O<sub>3</sub>/m<sup>3</sup> for 48 hours (Kamil'dzhanov, 1982). Similarly, motility was decreased after: (1) a 120-hour exposure to 7.95 mg/m<sup>3</sup>; (2) a 252-hour exposure to 1.45 mg/m<sup>3</sup>; and (3) an 800-hour exposure to 0.36 mg/m<sup>3</sup>.

Holson et al. (1999) administered arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) by whole body inhalation to groups of 25 Crl:CD (SD)BR female rats every day for six hours per day, beginning fourteen days prior to mating and continuing throughout mating. The target exposure levels were 0.3, 3.0, and 10.0 mg As<sub>2</sub>O<sub>3</sub>/m<sup>3</sup> (measured means: 0.24, 2.6, 8.3 mg As/m<sup>3</sup>). Maternal toxicity evidenced by the occurrence of rales, a decrease in net body weight gain, and decreased food intake during pre-mating and gestation exposure, was observed only at the high dose. The NOAEL for maternal toxicity was 2.6 mg As/m<sup>3</sup> (3.4 mg As<sub>2</sub>O<sub>3</sub>/m<sup>3</sup>). No treatment-related malformations or developmental variations were observed at any exposure level. The NOAEL for developmental toxicity was 8.3 mg As/m<sup>3</sup> (11 mg As<sub>2</sub>O<sub>3</sub>/m<sup>3</sup>). The median mass aerodynamic diameter of particle sizes generated in the exposure chambers ranged from 1.9 to 2.2 µm for the three doses indicating that the dusts were respirable. However there were no blood or urine arsenic analytical data to assess delivered doses.

Nemec et al. (1998) evaluated the developmental toxicity of inorganic arsenic in mice and rabbits. CD-1 mice (25/dose group) and New Zealand White rabbits (20/dose group) were gavaged with aqueous arsenic acid (H<sub>3</sub>AsO<sub>4</sub>) doses of 0, 7.5, 24, or 48 mg/kg-d on gestation days (GD) six through 15 (mice) or 0, 0.19, 0.75, or 3.0 mg/kg-d on GD six through 18 (rabbits). The animals were examined at necropsy (GD 18, mice; GD 29, rabbits). Treatment related maternal toxicity including mortality (2/25) was observed only in the highest dose administered to mice. Effects on maternal weight gain were noted only on GD 6-9 (P < 0.01) and GD 15-18 (P < 0.05) of the mid dose and on GD 6-9



( $p < 0.05$ ) of the low dose. While overall maternal weight gains were statistically significantly reduced only at the top dose there was an apparent negative trend in decreased GD18 body weights with increasing dose (56.2 g control, 54.9 g, 52.7g, 46.7g, respectively). While the authors identified a NOAEL for maternal toxicity of 7.5 mg/kg-d, the apparent negative trend noted above suggests that this may be a LOAEL (4.0 mg As/kg-d).

Statistically significant adverse effects on offspring growth or survival were seen only at the highest dose of 48 mg/kg-d. However, there was an apparent negative trend in the number of live fetuses per litter with increasing dose (12.3 control, 11.6, 11.0, 6.6, respectively). An increased incidence of resorptions per litter was seen in the 48 mg/kg-d dose group ( $P \leq 0.01$ ), (mainly early resorptions). Early and total resorptions showed an apparent positive trend (6.4% total control, 6.1%, 9.6%, 41.9%, respectively). Mean fetal weight showed an apparent negative trend (1.3 g control, 1.32 g, 1.23 g, 0.99 g, respectively). There were no statistically significant dose-related increases in the overall incidence of fetal malformations; however, the mean percent of litter malformation was about three-fold higher in the 48 mg/kg-d dose group than in the lower doses and control. The NOAEL for developmental toxicity would appear to be 7.5 mg/kg-d (4.0 mg As/kg-d).

Maternal toxicity in rabbits, including mortality, slight body weight loss, and clinical signs (decreased urination and defecation, occasional prostration and ataxia), occurred only at the high arsenic acid dose of 3.0 mg/kg-d. The number of does with decreased urination and defecation appeared to be slightly higher in the mid- and low-dose groups, but these effects may not have been treatment related and no effects on body weight were seen. At sacrifice on GD 29 maternal body weight appeared to be reduced in the high dose group. A significant loss in mean maternal gravid body weight occurred during the first six days of high-dose treatment (GD 6-12) ( $p \leq 0.01$ ). This effect persisted and was significantly different from controls for the entire treatment interval (GD 6-18). There were no statistically significant increases in the incidences of any developmental parameters, including malformations. Fetal survival, mean fetal weight, and sex ratio on GD 29 were not affected by the treatment. The number of live fetuses per litter was reduced and resorptions per litter increased in the high-dose group. The latter findings were mainly due to one doe with a totally resorbed litter. The overall values were the range from laboratory historical controls. The authors identified a NOAEL of 0.75 mg/kg-d (0.4 mg As/kg-d) for both maternal toxicity and developmental toxicity.

Stump et al. (1999) administered either sodium arsenate ( $\text{As}^{\text{V}}$ ) i.p. or arsenic trioxide ( $\text{As}^{\text{III}}$ ) i.p. or by gavage on GD 9 to 25 CrI:CD (SD) BR rats. The doses of sodium arsenate were 0, 5, 10, 20, and 35 mg/kg (0, 1.2, 2.4, 4.8, 8.4 mg As/kg). The doses of arsenic trioxide were: i.p. 0, 1, 5, 10, and 15 mg/kg (0, 0.8, 3.8, 7.6, and 11.4 mg As/kg); and by gavage (p.o.) 0, 5, 10, 20, 30 mg/kg (0, 3.8, 7.6, 15.2, 22.7 mg As/kg). Sodium arsenate (i.p.) caused decreased maternal food consumption (GD 9-20), decreased body weights and body weight gains at the highest dose of 35 mg/kg. Decreased food consumption was also seen in the 20 mg/kg dose group at GD 9-10 and GD 9-20. Arsenic trioxide (i.p.) resulted in excessive mortality in the highest dose-group (19/25)

and significant reductions in maternal food consumption, body weight at GD20, body weight change, and net body weight in the next highest dose-group (10 mg/kg). Arsenic trioxide (p.o.) resulted in less mortality in the highest dose-group (7/25). Clinical signs were noted in the 20 and 30 mg/kg dose-groups including changes in fecal consistency and decreased defecation. Food consumption (GD 9-10) was decreased in a dose-dependent manner across As treatment groups. The study identified single dose maternal effects NOAELs of 2.4 mg As/kg for sodium arsenate (i.p.) and 3.8 mg As/kg for arsenic trioxide i.p. A LOAEL of 3.8 mg As/kg was identified for arsenic trioxide p.o.

Intraperitoneal administration of sodium arsenate or arsenic trioxide caused neural tube and ocular defects (exencephaly, microphthalmia/anophthalmia, and other craniofacial defects) in the offspring of treated rats. These effects were statistically significant only at doses causing maternal toxicity or mortality (35 and 10 mg/kg, respectively). Oral administration of arsenic trioxide caused no treatment-related malformations. The study identified single dose developmental NOAELs of 2.4 mg As/kg for sodium arsenate i.p., 3.8 mg As/kg for arsenic trioxide i.p., and 15.2 mg As/kg for arsenic trioxide p.o.

DeSesso et al. (1998), in a comprehensive review of the developmental toxicity of inorganic arsenic, concluded that cranial neural tube defects (NTDs) were induced in rodents only when exposure occurred early in gestation, at high maternally toxic doses, and by parenteral routes of administration. They argued that such NTD effective doses are unlikely to be achieved by the oral, inhalation, or dermal routes in rodents, and that inorganic arsenic does not represent a realistic developmental risk in humans subjected to any environmentally relevant exposure scenarios.

Male and female Charles River CD mice (10/group) were treated with 0 or 5 ppm arsenite in drinking water continuously through three generations (Schroeder and Mitchener, 1971). Endpoints examined included the interval between litters, the age at first litter, the ratio of males to females, the number of runts, stillborn offspring, failures to breed, and congenital abnormalities. The study showed an alteration in the number of small litters in the arsenic exposed group.

Female CD-1 mice (8-15/group) were treated by oral gavage with 0, 20, 40, or 45 mg sodium arsenite/kg on a single day of gestation between days 8 and 15 (Baxley et al., 1981). Maternal mortality, fetal malformations, and increased prenatal death were observed among animals treated with 40 and 45 mg sodium arsenite/kg.

Pregnant golden hamsters (>10/group) were treated by oral gavage with a single administration of 0, 20, or 25 mg/kg sodium arsenite on one of gestational days 8-12 (Hood and Harrison, 1982). Prenatal mortality was increased among animals receiving 25 mg/kg on gestational days 8 and 12 and fetal weights were decreased among animals receiving 25 mg/kg on gestational day 12. One dam died following administration of 20 mg/kg.

Intravenous injection of radioactive arsenate (V) or arsenite (III) in several rodent species, including mice and hamsters, resulted in accumulation of arsenic in the lumen of

the epididymal duct, which suggested that long term exposure of sperm to arsenic may occur *in vivo* following acute exposure (Danielsson et al., 1984).

## **6. Chronic Toxicity of Arsenic and Arsenic Compounds**

### **6.1 Chronic Toxicity to Adult Humans**

Arsenic in drinking water is carcinogenic to humans (Group 1, IARC, 2004). Arsenic compounds show limited to sufficient evidence of carcinogenicity in experimental animals (IARC, 2004). The U.S. Environmental Protection Agency has classified arsenic as Group A; a human carcinogen, based on sufficient evidence from human data including increased lung cancer mortality in multiple human populations exposed primarily through inhalation, increased mortality from multiple internal organ cancers (liver, kidney, lung, bladder), and increased skin cancers observed in populations exposed to arsenic in drinking water (IRIS online file [www.epa.gov/iris/subst/0278.htm](http://www.epa.gov/iris/subst/0278.htm)). Since this document deals with noncancer risks, the carcinogenicity of arsenic is not covered here in any detail (see OEHHA (1999)).

#### **6.1.1 Inhalation Exposure**

Smelter workers, exposed to concentrations of arsenic up to 7 mg As/m<sup>3</sup>, showed an increased incidence in nasal septal perforation, rhinopharyngolaryngitis, tracheobronchitis, and pulmonary insufficiency (Lundgren, 1954).

In a case-control study, copper smelter workers (n = 47) exposed to arsenic for 8-40 years (plus 50 unexposed controls matched for age, medical history, and occupation) were examined by electromyography and for nerve conduction velocity in the arms and legs (Blom et al., 1985). The workers were found to have a statistically significant correlation between cumulative exposure to arsenic and reduced nerve conduction velocities in three peripheral nerves (upper and lower extremities). Slightly reduced nerve conduction velocity in 2 or more peripheral nerves was reported as “more common” among arsenic exposed workers. Minor neurological and electromyographic abnormalities were also found among exposed workers. Occupational exposure levels were estimated to be 0.05-0.5 mg As/m<sup>3</sup>, with As<sub>2</sub>O<sub>3</sub> the predominant chemical form. Except for three arsenic exposed workers who had long-term exposure to lead, exposure to other heavy metals was insignificant.

The smelter workers described by Blom et al. (1985) (number of controls reduced to 48) were further examined for prevalence of Raynaud’s phenomenon and for vasospastic tendency by measurement of finger systolic pressure at 10°C and/or 15°C relative to that at 30°C (FSP%) (Lagerkvist et al., 1986). The FSP% was found to covary with the duration of exposure to arsenic, and the prevalence of Raynaud’s phenomenon was significantly increased among exposed workers. Daily arsenic uptake was estimated at less than 300 µg/day and was confirmed with urinary excretion data.

Hyperpigmentation and hyperkeratinization were observed in workers exposed to 0.4 - 1 mg/m<sup>3</sup> inorganic arsenic for two or more years (Perry et al., 1948).

### 6.1.2 Oral Exposure

Most of the relevant epidemiological data on arsenic adverse effects comes from studies of arsenic exposure via drinking water. These studies are relevant because arsenic exerts similar toxic effects once it enters the body. For example, arsenic causes lung cancer in humans by both oral and inhalation routes. The adverse effects summarized below include skin lesions(keratoses and altered pigmentation), vascular effects on the heart, brain and peripheral vasculature, peripheral neuropathy, and lung disease.

#### 6.1.2.1 Skin Effects

Mazumder et al. (1998) investigated arsenic-associated skin lesions of keratosis and hyperpigmentation in 7683 exposed subjects in West Bengal, India. While water arsenic concentrations ranged up to 3400 µg/L, over 80% of the subjects were consuming water with < 500 µg/L. The age-adjusted prevalence of keratosis was strongly related to water As concentration, rising from zero in the lowest exposure level (< 50 µg/L) to 8.3% for females drinking water containing >800 µg As/L, and from 0.2 to 10.7% in males, respectively. A similar dose-response was observed for hyperpigmentation: 0.3 to 11.5% for females; and 0.4 to 22.7% for males. Overall males had 2-3 times the prevalence of both keratosis and hyperpigmentation than females apparently ingesting the same doses of arsenic per body weight. Subjects that were more than 20% below standard body weight for their age and sex had a 1.6-fold increase in the prevalence of keratoses, suggesting that malnutrition may play a role in increasing susceptibility.

Rahman et al. (2006) evaluated arsenic exposure and age- and sex-specific risk for skin lesions in a population-based case-referent study in Bangladesh. The entire population over four years of age of Matlab, Bangladesh (N = 166,934) was screened for skin lesions. Skin lesions were classified as hyperpigmentation (melanosis), hypopigmentation (leukomelanosis), or keratosis. A total of 504 cases with skin lesions were identified. A randomly selected referent group of 1830 subjects was included in the study. Arsenic exposure was assessed by personal history of tube well use since 1970 or year of birth if later. Water samples from all functioning tube wells were measured for arsenic concentration by hydride-generation atomic absorption spectroscopy. A dose-response relationship was observed for increased skin lesions and arsenic exposure for both sexes (P < 0.001). For males using the metric of As µg/L the highest exposure quintile (≥ 300 µg/L) gave an adjusted odds ratio (OR) of 9.56 (95% CI = 4.20-21.8). Females gave a corresponding OR of 6.08 (3.06-15.5). The cumulative As exposure metric (µg/L x years) gave OR's of 10.4 and 9.19, respectively. In an analysis with males and females combined, adjusted for age and socioeconomic status, males had significantly higher risk of As-related skin lesions than females, when females' lowest average exposure quintile was used as the reference. For the highest quintile, the males OR was 10.9 (5.8-20.4) and the females OR was 5.78 (3.10-10.8), P = 0.005.

Dermatitis and irritation of the mucous membranes have been observed in arsenic-exposed workers (Vallee et al., 1960). Hepatic fatty infiltration, central necrosis, and cirrhosis were observed in two patients who ingested As<sub>2</sub>O<sub>3</sub> (1% in Fowler's solution) for three or more years (Morris et al., 1974). Daily consumption of 0.13 mg As/kg in contaminated well water resulted in the chronic poisoning and death of four children; at

autopsy, myocardial infarction and arterial thickening were noted (Zaldivar and Guillier, 1977).

#### 6.1.2.2 Vascular Disease

Vascular diseases have long been noted to be associated with chronic arsenic exposures among German vineyard workers (Grobe, 1976) and inhabitants of Antofagasta, Chile (Borgono et al., 1977). Peripheral vascular diseases have been reported to be associated with the occurrence of arsenic in well waters in Taiwan (Chen and Wu, 1962; Chi and Blackwell, 1968; Tseng, 1977; Chen et al., 1988). Concentrations in one study were characterized as 0.10 – 1.8 ppm (Yu et al., 1984). The term arseniasis or arsenosis connotes vascular disease associated with chronic exposure to arsenic, specifically blackfoot disease (BFD). BFD is characterized by progressive narrowing of the peripheral arteries, particularly those of the lower extremities. This can lead to ulceration, gangrene and amputation. The etiology of BFD is unclear but arsenic is thought to be the principal cause. The term arsenicosis refers to arsenic induced skin lesions ranging in severity over four stages, seven grades and 20 sub-grades from diffuse melanosis (skin pigmentation or depigmentation) to aggressive skin and internal malignancy (Saha, 2003).

Wu et al. (1989) found significant trends of mortality rates from peripheral vascular diseases and cardiovascular diseases with concentrations of arsenic in well water. However, no significant association was observed for cerebrovascular accidents. Engel and Smith (1994) evaluated arsenic in drinking water and mortality from vascular disease in 30 U.S. counties from 1968 to 1984. Mean As levels in drinking water ranged from 5.4 to 91.5 µg/L. Standardized mortality ratios (SMRs) for diseases of arteries, arterioles, and capillaries (DAAC) for counties exceeding 20 µg/L were 1.9 (90% C.I. = 1.7-2.1) for females and 1.6 (90% C.I. = 1.5-1.8) for males. SMRs for three subgroups of DAAC including arteriosclerosis and aortic aneurysm were also elevated as were congenital abnormalities of the heart and circulatory system.

Tseng et al. (1996) studied the dose relationship between peripheral vascular disease (PVD) and ingested inorganic arsenic in blackfoot disease endemic villages in Taiwan. A total of 582 adults (263 men and 319 women) underwent Doppler ultrasound measurement of systolic pressures on bilateral ankle and brachial arteries and estimation of long-term arsenic exposure. The diagnosis of PVD was based on an ankle-brachial index of < 0.9 on either side. Multiple logistic regression analysis was used to assess the association between PVD and As exposure. A dose-response relationship was observed between the prevalence of PVD and long-term As exposure. The odds ratios (95% confidence intervals) after adjustment for age, sex, body mass index, cigarette smoking, serum cholesterol and triglyceride levels, diabetes mellitus and hypertension were 2.77 (0.84-9.14), and 4.28 (1.26-14.54) for those who had cumulative As exposures of 0.1 to 19.9 and ≥ 20 (mg/L) x yr, respectively. A follow up study (Tseng et al., 1997) indicated that PVD was correlated with ingested As and not with abnormal lipid profiles. The lipid profiles studied were total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c), apolipoprotein AI, and apolipoprotein B. Other lipids such as modified LDL, subclasses of LDL and HDL, and

other lipoproteins such as lipoprotein (a), which may track as better indicators of atherosclerosis, were not included. Also, the roles of platelet aggregation and coagulation profiles were not studied.

Chen et al. (1996) evaluated the dose-response relationship between ischemic heart disease (ISHD) mortality and long-term arsenic exposure. Mortality rates from ISHD among residents in 60 villages in an area of Taiwan with endemic arseniasis from 1973 through 1986 were analyzed for association with As concentrations in drinking water. Based on 1,355,915 person-years and 217 ISHD deaths, the cumulative ISHD mortalities from birth to age 79 yr were 3.4%, 3.5%, 4.7%, and 6.6% for the median As concentrations of < 0.1, 0.1-0.34, 0.35-0.59, and  $\geq 0.6$  mg/L, respectively. Multivariate-adjusted relative risks (RRs (95% C.I.)) associated with cumulative arsenic exposure from well water were 2.46 (0.53-11.36), 3.97 (1.01-15.59), and 6.47 (1.88-22.24) for 0.1-9.9, 10.0-19.9, and 20+ (mg/L)-yr, respectively, compared with those without As exposure.

Chiou et al. (1997b) evaluated the dose-response relationship between prevalence of cerebrovascular disease and ingested arsenic among residents of the Lanyang Basin in northeast Taiwan. A total of 8102 adults from 3901 households were recruited for the study. Arsenic in well water of each household was determined by hydride generation and atomic absorption spectrometry. Logistic regression analysis was used to estimate multivariate-adjusted odds ratios and 95% confidence intervals for various risk factors of cerebrovascular disease. A significant dose-response relationship was observed between As concentration in well water and prevalence of cerebrovascular disease after adjustment for age, sex, hypertension, diabetes mellitus, cigarette smoking, and alcohol consumption. The dose-response relationship was even more prominent for cerebral infarction with multivariate-adjusted odds ratios (95% C.I.) of 1.0, 3.4 (1.6-7.3), 4.5 (2.0-9.9), and 6.9 (3.0-16), respectively, for those who consumed well water with As concentrations of 0, 0.1-50.0, 50.1-299.9, and  $> 300$   $\mu\text{g/L}$ . For cumulative arsenic exposures of  $< 0.1$ , 0.1-4.9, and  $\geq 5.0$  (mg/L)-yr, the odds ratios were 1.00, 2.26, and 2.69 for cerebrovascular disease and 1.00, 2.66, and 3.39 for cerebral infarction, respectively. All of the values above for As exposed groups were significantly greater than unexposed at  $P < 0.05$ .

Chen et al. (1995) also investigated the association between long-term exposure to inorganic arsenic and the prevalence of hypertension. A total of 382 men and 516 women were studied in villages where arseniasis was endemic. Hypertension was defined as a systolic blood pressure of 160 mm Hg or greater, or a history of hypertension treated with antihypertensive drugs. The long-term arsenic exposure was calculated from the history of artesian well water consumption obtained through subject questionnaires and the measured arsenic concentration in well water. Residents in villages where long-term arseniasis was endemic had a 1.5-fold increase in age- and sex-adjusted prevalence of hypertension compared with residents in nonendemic areas. The duration of well water consumption, average As water concentration, and cumulative As exposure were all significantly associated with hypertension. For the cumulative As exposure in (mg/L)-yr, the percent prevalence values were: 0, 5.0%; 0.1-6.3 (mg/L)-yr, 4.9%; 6.4-

10.8 (mg/L)-yr, 12.8%; 10.9-14.7 (mg/L)-yr, 22.1%; 14.8-18.5 (mg/L)-yr, 26.5%; > 18.5 (mg/L)-yr, 29.2%.

As part of a study of arsenic exposure via drinking water and mortality outcome in Millard County, Utah, Lewis et al. (1999) found a statistically significant association with mortality from hypertensive heart disease. Median drinking water concentration of arsenic ranged from 14 to 166 µg/L for the 946 subjects in the study. The standard mortality ratios (SMR) without regard to specific exposure levels were SMR = 2.20 (95% C.I., 1.36-3.36) for males and SMR = 1.73 (95% C.I., 1.11-2.58) for females. When analyzed by cumulative exposure groups of low (< 1.0 (mg/L)-yr), medium (1.0-4.9 (mg/L)-yr), and high (≥ 5.0 (mg/L)-yr), there was no apparent dose response relationship. However the cumulative dose estimates in this study were lower than in the Chen et al. (1995) discussed above so the results of the two studies are not inconsistent.

Chen *et al.* (2006) conducted a cross-sectional analysis of the association of arsenic exposure from drinking water and blood pressure in 10,910 subjects. Time-weighted well arsenic concentrations (TWA) based on current and past well usage were derived. Odds ratios (OR's) for high pulse pressure (systolic – diastolic pressure ≥ 55 mmHg) by increasing TWA quintiles (≤ 8, 8.1-40.8, 40.9-91.0, 91.1-176.0, 176.1-864.0 µg/L) were: 1.00 (referent); 1.39 (95% C.I. 1.14, 1.71); 1.21 (0.9, 1.49); 1.19 (0.97, 1.45); 1.19 (0.97, 1.46). OR's for systolic hypertension (≥ 140 mmHg) suggested a similar but weaker association. Participants with lower than average intake of B vitamins and folate showed somewhat higher OR's. No associations were apparent for TWA and diastolic hypertension.

In a study related to those above, Lai et al. (1994) studied inorganic arsenic ingestion and the prevalence of diabetes mellitus. A total of 891 adult residents of villages in southern Taiwan where arseniasis is endemic were included in the study. Diabetes status was determined by an oral glucose tolerance test and a history of diabetes regularly treated with sulfonylurea or insulin. Cumulative arsenic exposure in ppm-yr was determined from the detailed history of drinking artesian well water. There was a dose-response relation between cumulative arsenic exposure and prevalence of diabetes mellitus. The relation remained significant after adjustment for age, sex, body mass index, and activity level at work by a multiple logistic regression analysis giving multivariate-adjusted odds ratios of 6.61 and 10.05, respectively, for exposures of 0.1-15 ppm-yr and > 15.0 ppm-yr versus an unexposed group. In an effort to confirm this association between diabetes mellitus and arsenic observed for drinking water in Taiwan, Rahman and Axelson (1995) reviewed 1978 case-control data from a Swedish copper smelter. Twelve cases of diabetes mellitus (death certificate) were compared with 31 controls without cancer, cardiovascular and cerebrovascular disease. The odds ratios for diabetes mellitus with increasing arsenic exposure categories were 1.0 (reference level), 2.0, 4.2, and 7.0 with the 95% confidence level including unity. The trend was weakly significant,  $p = 0.03$ . Albeit with limited numbers, the study provides some support for a role of arsenic exposure in the development of diabetes mellitus.

#### 6.1.2.3 Neurological Disease

Hafeman et al. (2005) evaluated the association between arsenic exposure and peripheral neuropathy in a cross-sectional study of 137 adults in Bangladesh. Exposure measures included individual arsenic water concentration, cumulative arsenic index (CAI), and urinary arsenic concentration. Experimental measures were primarily vibrotactile threshold testing of the index finger (IVT) and toe (TVT) and secondarily tapping speed, grip strength, ankle reflex, and proprioception. The cumulative arsenic index and urinary arsenic were both significantly associated with elevated TVT ( $P = 0.02$  and  $P = 0.009$ , respectively) after adjustment for age and gender. While dose-response relations were difficult to define, a linear regression analysis of TVT (vibration units) versus the continuous measures of urinary arsenic and CAI gave slopes of 0.02 and 0.0025 TVT units/50  $\mu\text{g As/mg}$  urinary creatinine, respectively. The association between IVT and arsenic exposure was not statistically significant. No association was found between any measure of arsenic exposure and grip strength, tapping speed, ankle reflex, or proprioception.

#### 6.1.2.4 Lung Disease

Von Ehrenstein et al. (2005) studied the relation between lung function, respiratory symptoms, and arsenic in drinking water among 287 adults, including 132 with arsenic-induced skin lesions in West Bengal, India. Arsenic levels in drinking water and the number of male subjects with or without skin lesions were: 0-99  $\mu\text{g/L}$ , 9, 36; 100-399  $\mu\text{g/L}$ , 66, 34;  $\geq 400$   $\mu\text{g/L}$ , 18, 15, respectively. For respiratory symptoms of “shortness of breath at night” and “morning cough”, the odds ratios (ORs) for men with skin lesion versus those without was 2.8 with 95% confidence intervals (C.I.) of (1.1, 7.6) and (1.2, 6.6), respectively. For men with skin lesions, the average forced expiratory volume in one second ( $\text{FEV}_1$ ) was reduced by 256.2 mL (95% C.I.; 113.9, 398.4)  $P < 0.001$ . Average forced vital capacity (FVC) was reduced by 287.8 mL (95% C.I.; 134.9, 440.8)  $P < 0.001$ . In men a 100  $\mu\text{g/L}$  increase in arsenic level was associated with a 45.0 mL decrease (95% C.I.; 6.2, 83.9) in  $\text{FEV}_1$  ( $P = 0.02$ ) and a 41.4 mL decrease (95% C.I.; -0.7, 83.5) in FVC ( $P = 0.054$ ). Women participating in the study ( $N = 109$ ) had a lower risk of developing skin lesions than men and exhibited few respiratory symptoms.

## 6.2 Chronic Toxicity to Infants and Children

The adverse effects of inorganic arsenic exposure reported in children include skin lesions, neurodevelopmental effects (IQ and related effects), lung disease expressed in later years, and reproductive effects (decreased birth weight, spontaneous abortion, neonatal death).

### 6.2.1 Skin Effects

As noted above Mazumder et al. (1998) observed a dose-response for arsenic-associated skin lesions in a cross-sectional survey of 7683 subjects in West Bengal, India. The study population was divided by age decades such that the effect on young children ( $\leq 9$  yr) and adolescents (10-19 yr) could be analyzed separately. The prevalence of keratosis in females and males was 0.2 and 0.5 percent in young children and 1.0 and 1.7 percent in adolescents, respectively. The comparable values for hyperpigmentation were 1.7 and 2.0 percent and 2.2 and 3.5 percent, respectively. Overall 1149 young children and 1599



adolescents were surveyed. The low- to mid-dose quantal responses for combined skin lesions in young children using the mid points of the arsenic concentration ranges ( $\mu\text{g/L}$ ) were: 25, 0/414; 75, 0/95; 125, 4/118; 175, 2/50; 275, 6/161; 425, 11/101. For the adolescents the comparable values were: 1/730; 2/147; 2/107; 7/110; 26/213; 9/58.

### 6.2.2 Neurodevelopmental Effects

The adverse effects of inorganic arsenic on the developing intellectual function of exposed children have been reported in several studies summarized in this section. While some of the studies have deficiencies, as a group they indicate that arsenic exposure, like lead exposure, presents a higher risk to children than adults. The neurodevelopmental endpoint has been selected by OEHHA as the critical effect for deriving 8-hour and chronic RELs for inorganic arsenic.

Calderon et al. (2001) conducted a cross-sectional study to examine the effects of chronic exposure to lead (Pb) and arsenic (As), and also nutrition, on the neuropsychological development of children. Two populations of children aged six to nine years ( $N = 41, 39$ ) with differing As exposure levels (63 vs. 40  $\mu\text{g/g}$ ) but similar Pb exposures (8.9 vs. 9.7  $\mu\text{g Pb/dL}$  blood, respectively) were compared using the Wechsler Intelligence Scale for Children (WISC) Revised Version for Mexico. After controlling for significant potential confounders verbal IQ was observed to decrease with increasing urinary arsenic ( $P < 0.01$ ). Language, verbal comprehension and long-term memory also appeared to be adversely affected by increasing arsenic exposure (concepts and knowledge factors,  $P < 0.05$  each). Blood lead was significantly associated with a decrease in attention (sequential factor,  $P < 0.05$ ). However since blood lead is an imprecise measure of lead burden there could be some residual confounding in this study.

The relationship between arsenic exposure via drinking water and neurological development as indicated by intelligence (IQ) was assessed in Thailand (Siripitayakunkit et al., 1999) in 529 children aged six to nine years using a cross-sectional design. Arsenic levels in hair were used to assess exposure and the WISC test for children was used to assess IQ. The range of arsenic concentrations in hair was 0.48 to 26.94  $\mu\text{g/g}$  (mean = 3.52, SD = 3.58). The mean IQ of the study was 90.44 (range 54 to 123). Most of the IQs were classified as average (45.7%) or dull normal (31.6%). Approximately 14% and 3% of the children were in the borderline and mental defective groups, respectively. The percentage of children in the average IQ group decreased significantly from 57 percent to 40 percent with increasing arsenic exposure. The percentage in the lower IQ group increased with increasing As (23% to 38%) and in the low IQ group (zero to six percent). In a comparison of IQ between children with As hair levels  $\leq$  two ppm or  $>$  two ppm, arsenic was found to explain 14 percent of the variance in IQ after controlling for father's occupation, mother's intelligence score, and family income. Arsenic levels in hair above 2 ppm were associated with a 0.75-point decrease in IQ below the grand mean and As levels above 5 ppm with a two point decrease. Although the cross-sectional study design does not allow for establishment of the time precedence of exposure to arsenic, the investigators stated that the subjects of the study were born in a period of chronic arsenic poisoning and that this cohort has been continuously exposed since birth due to their non-mobility. The study suffers from small numbers of children exposed to low arsenic (hair

arsenic  $\leq 1$  ppm) so this group could not be compared to the high arsenic children. Also the possible exposure to chemical confounders like lead was not discussed.

In a parallel cross-sectional study (Siripitayakunkit et al., 2001) the 529 children (above) were subjected to the Motor-Free Visual Perception Test (MVPT) and the Visual-Motor Integration Test (VMI). The visual perception score of each child was compared with the score of children in a control sub-district of the same age. The cutoff point for poor perception was the mean minus one standard deviation (SD) in each age level. Among arsenic-exposed children, 21 percent had poor visual perception and 17.6 percent had poor VMI. The comparable values in the control population were 16.5 percent and 15.8 percent, respectively. Potential confounders were controlled by multiple classification analysis. Only five percent of the variance in visual perception of children was significantly explained by arsenic ( $P = 0.01$ ). The grand mean perception score was 20.57 and the adjusted values at low, medium and high hair As were 20.92, 20.51, and 20.03, respectively. Alternatively, these authors did not find an effect of arsenic on visual-motor integration.

Like the study of IQ decrements noted above, this study has the advantage of associating an adverse effect in children with a metric of chronic arsenic exposure, hair arsenic concentration. Disadvantages include a limited level of reporting and possible confounding with exposure to other metals.

Tsai et al. (2003) performed a cross-sectional study of the effect of arsenic exposure on the development of cognitive function among adolescents. Forty-nine 13-year old students were divided into low and high exposure groups and were compared with 60 13-year old unexposed children. Four neurobehavioral tests were conducted: continuous performance test (CPT); symbol digit (SD); pattern memory (PM); and switching attention (SA). Exposure in terms of As concentration in drinking water averaged 0 ( $<0.15$ ), 131.2, and 185.0 ppb for control and exposure groups, respectively. Average cumulative arsenic exposures were 0, 252.1, and 768.2 mg (e.g.,  $184.99 \text{ ppb} \times 1008.6 \text{ cm}^3/\text{d} \times 11.28 \text{ yr} \times 365 \text{ d/yr} \times 10^{-3}$ ). Neurobehavioral analysis revealed significant dose-response effects of arsenic exposure on CPT ( $P = 0.005$ ), PM ( $P = 0.009$ ) and SA ( $P = 0.0001$ ), but not on SD ( $P = 0.23$ ). A multiple linear regression analysis of the dose-response relationship between cumulative arsenic exposure and neurobehavioral endpoints showed a strong arsenic effects for CPT (low exposure group,  $P = 0.001$ ), PM (high exposure group,  $P = 0.003$ ) and SA (high and low exposures,  $P = 0.0001$ ). This study is limited by low numbers but seems in line with other findings of As-induced CNS effects. The authors note that “the central nervous system of child and adolescents might be more vulnerable than adult to neurotoxicant”. Although no dose-response relationship between As exposure and nerve conduction velocities was observed, the authors could not exclude the possibility of peripheral nerve dysfunction.

Wasserman et al. (2004) conducted a cross-sectional study of intellectual function in 201 As-exposed 10-year old children in Bangladesh. Children’s intellectual function was assessed with tests drawn from the Wechsler Intelligence Scale for Children version III including Verbal, Performance, and Full-Scale raw scores. Children provided urine for

arsenic and creatinine and blood samples for blood lead and hemoglobin measurements. After adjustment for sociodemographic covariates and waterborne levels of manganese (Mn), As in drinking water was associated with reduced intellectual function, in a dose-dependent manner. Children exposed to water arsenic of  $> 50 \mu\text{g/L}$  had significantly lower Performance and Full-Scale scores than did children with water As levels  $< 5.5 \mu\text{g/L}$ . Using the Full-Scale raw score, As water concentrations of 10 and  $50 \mu\text{g/L}$  were associated with decrements of 3.8 and 6.4 points, respectively. The relationships between urinary arsenic concentration ( $\mu\text{g As/g creatinine}$ ) and child intellectual function were not statistically significant but were in the expected (negative) direction (Full-Scale,  $P = 0.09$ ; Performance,  $P = 0.14$ ; Verbal,  $P = 0.11$ ). Since there was no standard of intelligence for use in Bangladesh these decrements could not be directly equated with U.S. standard IQ points. However, “other simpler predictors of child intellectual function, such as maternal education and child height and head circumference, were significantly related to intellectual raw scores in the expected directions.” In this study, as in others of this type exposure is inferred from water concentration.

### 6.2.3 Lung Effects

Smith et al. (1998) studied lung and urinary bladder cancer mortality in a region of northern Chile (Antofagasta) where the residents were exposed to arsenic in their drinking water. Arsenic levels ranged from a population weighted average of  $570 \mu\text{g/L}$  between 1955 and 1969 to  $100 \mu\text{g/L}$  by 1980. The mortality ratios (observed/expected deaths) for bladder, kidney, liver, and skin cancers, and all other cancers combined, were not related to age in either sex. However, lung cancer mortality ratios were particularly high in younger men aged 30-39 yr (SMR = 11.7, 95 percent C.I. 6.4-19.6,  $P < 0.001$ ). Also observed was a decreasing trend in chronic obstructive pulmonary disease deaths (COPD), with higher rates among younger men, particularly those aged 30-39. Four COPD deaths were reported among men (0.8 expected), and six deaths among women (0.1 expected). These ten individuals who died of COPD would have been young children at the time of peak arsenic water levels in 1955-1970.

In a later study Smith et al. (2006) reported increased mortality from lung cancer and bronchiectasis in young adults following arsenic exposures *in utero* and in early childhood. For subjects born just before the high exposure period (1950-1957) and exposed in early childhood the SMR for bronchiectasis was 12.4 (95% C.I., 3.3-31.7;  $P < 0.001$ ). For those born during the high exposure period (1958-1970) with likely *in utero* and early childhood exposure the SMR for bronchiectasis was 46.2 (C.I., 21.1-87.7;  $P < 0.001$ ). The authors conclude that “exposure to arsenic in drinking water during early childhood or *in utero* has pronounced pulmonary effects, greatly increasing subsequent mortality in young adults from both malignant and nonmalignant lung disease.”

Additional evidence supporting a link between childhood arsenic exposure and subsequent lung disease comes from autopsies of children in the affected area. The results of five autopsies of children, who died in 1968 and 1969 in Antofagasta and showed skin lesions and other evidence of arsenic poisoning, also showed lung abnormalities in four of the children. Two of these cases exhibited interstitial fibrosis (Rosenberg, 1974). Also, a survey of 144 children in Antofagasta with skin pigmentation

due to arsenic exposure reported a history of bronchopulmonary disease 2.5-fold more frequent than children with normal skin (15.9 vs. 6.2 percent, respectively) (Borgono et al., 1977).

#### **6.2.4 Reproductive and Other Effects**

Chronic exposure to arsenic has been associated with decreased birth weight and an increased rate of spontaneous abortion in female smelter workers. However, this association is confounded by the presence of other toxicants in the smelting process, including lead (Nordstrom et al., 1979). Anemia and leukopenia have been reported in infants ingesting approximately 3.5 mg As/day in contaminated milk over a period of 33 days (Hammamoto, 1955).

Premature birth and subsequent neonatal death was reported in a single individual following ingestion of arsenic (Lugo et al., 1969).

Ihrig et al. (1998) conducted a hospital-based case-control study of stillbirths and environmental arsenic exposure using an atmospheric dispersion model linked to a geographical information system. They collected data on 119 cases and 267 controls in a central Texas area including a facility with 60-year history of arsenic-based agricultural product manufacture. Four exposure groups were categorized (0; < 10 ng/m<sup>3</sup>; 10-100 ng/m<sup>3</sup>; and > 100 ng/m<sup>3</sup>). For the period 1983-93 they fit a conditional logistic regression model including maternal age, race/ethnicity, parity, income group, exposure as a categorical variable, and exposure-race/ethnicity interaction. Effects were only seen in the Hispanic group with the medium exposure group having a prevalence odds ratio and 95% confidence interval of 1.9 (0.5-6.6) and the high exposure group 8.4 (1.4-50.1). The authors postulate a possible influence of a genetic polymorphism affecting folate metabolism in Hispanic populations possibly leading to increased neural tube defects and stillbirths. Small numbers limits this study; for example, there were only seven cases in the high exposure group and five of these were Hispanic.

Von Ehrenstein et al. (2006) studied pregnancy outcomes, infant mortality, and arsenic exposure via drinking water in West Bengal, India. The reproductive histories of 202 women were reviewed including measurements of 409 drinking water wells. The total number of pregnancies was 660 and the number of live births plus stillbirths was 558. Odds ratios for spontaneous abortion, stillbirth, neonatal mortality (death in the first month) and infant mortality (death in the first year) were estimated by logistic regression. Exposure to arsenic concentrations  $\geq 200$   $\mu\text{g/L}$  during pregnancy was associated with a six-fold increased risk of stillbirth after adjustment for potential confounders (OR = 6.07; 95% C.I. 1.24-24.0,  $p = 0.01$ ). The odds ratio for neonatal death was 2.81 (95% C.I. 0.73-10.8). No significant associations were found for arsenic exposure and spontaneous abortion (OR = 1.01; 95% C.I. 0.38-2.70) or overall infant mortality (OR = 1.33; 95% C.I. 0.43-4.04). Arsenic related skin lesions were observed in 12 women who had increased risk of stillbirth (OR = 13.1; 95% C.I. 3.17-54.0).

### 6.3 Subchronic and Chronic Toxicity to Experimental Animals

Female albino rats (20 per group) were exposed to 0, 1.3, 4.9, or 60.7  $\mu\text{g As}_2\text{O}_3/\text{m}^3$  as aerosol continuously for 3 months (Rozenshtein, 1970). Decreased whole blood sulfhydryl group content, histological changes in the brain, bronchi, and liver, changes in conditioned reflexes, and changes in chronaxy ratio were observed in both the high- and mid-dose groups. Among animals in the high dose group, eosinophilia, decreased blood cholinesterase activity, decreased serum sulfhydryl content, and increased blood pyruvic acid were observed. No significant changes were observed in the low-dose group.

Male mice (8-10 per group) were exposed to 0, 0.5, 2.0, or 10.0 ppm sodium arsenite in drinking water for 3 weeks followed by a 28-day recovery period (Blakley et al., 1980). The primary immune response of the spleen (as indicated by changes in IgM-production assayed by plaque-formation) was suppressed at all dose levels. The secondary immune response was also suppressed at all dose levels as indicated by a decrease in the number of IgG producing cells.

Male Sprague-Dawley rats (7-28 per group) were exposed to 0, 40, 85, or 125 ppm sodium arsenate in drinking water for 6 weeks (Brown et al., 1976). Rats from all arsenic exposed groups showed increased relative kidney weights, decreased renal mitochondrial respiration, and ultrastructural changes to the kidney.

Male ddY mice (number not stated) received 0, 3, or 10 mg  $\text{As}_2\text{O}_3/\text{kg/day}$  orally for 14 days and were examined for changes in concentrations of monoamine-related substances in various brain regions and for changes in locomotor activity (Itoh et al., 1990). Locomotor activity was increased in the low-dose group and decreased in the high-dose group. Several monoamine-related compounds were altered in both dose groups in the cerebral cortex, hippocampus, hypothalamus, and corpus striatum. The study indicates an effect of arsenite on brain chemistry but is inconclusive with respect to dose response.

Male and female Wistar rats (7-10 per group) were treated from age 2 to 60 days by oral gavage with daily administration of 0 or 5 mg As/kg body weight (as sodium arsenate) (Nagaraja and Desiraju, 1993; 1994). After 160 days, body weights, brain weights, and food consumption were decreased in the arsenic exposed group. Acetylcholinesterase (AChE) and GAD activity and GABA levels were decreased in the hypothalamus, brain stem, and cerebellum during the exposure period; all but AChE activity returned to normal during the post-exposure period. Changes in operant conditioning were also observed among the exposed animals.

Female Holtzman rats (>5 per group) were treated with 0, 100, 500, 1000, 2000, or 5000 ppm  $\text{As}_2\text{O}_3$  in feed for 15 days (Wagstaff, 1978). Hexibarbitone sleeping time was altered in all arsenic exposed groups. Body weight and feed consumption were decreased among animals in the groups exposed to  $\geq 500$  ppm  $\text{As}_2\text{O}_3$ . Clinical signs of toxicity observed among arsenic exposed animals included roughened hair, diarrhea, and decreased physical activity.

Male Sprague-Dawley rats and C57 black mice (12 per group) were treated with 0, 20, 40, or 85 ppm sodium arsenate in drinking water for up to 6 weeks (Woods and Fowler, 1978). Among arsenic exposed rats, heme synthetase activity was decreased in all exposed groups. Among animals exposed to  $\geq 40$  ppm sodium arsenate, hepatic ALA synthetase activity was decreased and urinary uroporphyrin and coproporphyrin were increased. Among exposed mice, heme synthetase activity was decreased and uroporphyrinogen I synthetase activity was increased in all exposed groups. Among animals exposed to  $\geq 40$  ppm sodium arsenate, urinary uroporphyrin and coproporphyrin were increased.

Administration of 3.7 mg  $\text{As}_2\text{O}_3$ /kg/day to Rhesus monkeys for 12 months did not result in any neurologic change detectable by an EEG (Heywood and Sortwell, 1979). Two of the 7 animals exposed to this concentration died before the conclusion of the 52-week period. Of the surviving animals, two were retained for a 52-week recovery period after which they were sacrificed and necropsied. No significant changes in organ weights or gross appearance were noted.

## **7. Toxicity of Arsine**

### **7.1 Toxicity to Adult Humans**

Numerous case reports of accidental arsine poisoning exist in the literature, but reliable estimates of concentrations following acute human intoxication do not exist. This is due in large part to the insidious nature of arsine toxicity - arsine is a colorless gas, has a mild odor at low concentrations, produces no mucous membrane irritation, and usually results in delayed symptoms of toxicity (Klimecki and Carter, 1995). In mammalian systems, arsine primarily targets the erythrocyte and causes hemolysis and methemoglobinemia with acute exposure (NRC, 1984). Jaundice, hemoglobinuria, anuria, hepatic and renal damage, anoxia, and anemia are secondary effects resulting from hemolysis. Before the advent of dialysis, there were no reports of patients surviving if renal failure developed (Buchanan, 1962). Other acute symptoms reported include headache, weakness, dizziness, dyspnea, nausea, vomiting, diarrhea, and abdominal cramping (Klimecki and Carter, 1995). Central and peripheral nervous systems may be affected by acute arsine exposure, leading to agitation, disorientation, hallucinations, psychopathologic abnormalities, and peripheral nerve degeneration (Frank, 1976; Klimecki and Carter, 1995). The psychopathologic and peripheral abnormalities are thought to be secondary to the conversion of arsine to arsenate or arsenite. The first signs and symptoms of toxicity, hemoglobinuria and/or nausea, are usually delayed 2 to 24 hours following exposure (Kleinfeld, 1980).

A case report documents hemolytic anemia, hematuria, and renal failure following intermittent exposure to arsine gas over 2.5 hours (Parish et al., 1979). Symptoms of gastrointestinal distress, headache, and malaise were also reported following this exposure. The concentration of arsine gas sampled 3 days after exposure was 0.1 ppm ( $0.3 \text{ mg/m}^3$ ), but the concentration at the time of poisoning was unknown. Another typical accidental poisoning resulted when 2 men were exposed to arsine gas in a metal smelting works (Coles et al., 1969). Symptoms included nausea, vomiting, red urine, generalized

aching, shivering, epigastric pain, and jaundice. However, the more severely affected worker developed symptoms within 1 hour of exposure while the other did not develop symptoms for 24 hours. The more severely affected worker developed acute renal failure that required peritoneal dialysis.

In an occupational study, the highest average concentration of arsine recorded in a battery formation area of a battery manufacturing plant was  $20.6 \mu\text{g}/\text{m}^3$  (0.006 ppm) (Landrigan et al., 1982). Elevated levels of urinary arsenic were observed in some workers but effects on the hematopoietic system were apparently not examined.

A study by Williams et al. (1981) collected personal and area air samples after 2 workers exhibited symptoms of arsine poisoning while restoring a large 19th century painting. Symptoms included headaches, nausea, weakness, vomiting, and red urine. The blank-corrected air concentration of arsine ranged from 0.010 to  $0.067 \text{ mg}/\text{m}^3$ . While these concentrations are below the OSHA PEL 8-hour TWA of  $0.2 \text{ mg}/\text{m}^3$ , the results may indicate that these workers are sensitive responders or that humans in general may be more sensitive to the effects of arsine than experimental animals. However, the air samples may not represent the actual concentration of arsine that caused the symptoms of poisoning in the workers since the workplace air was not analyzed for arsine until after symptoms were reported. The study also notes that ‘appreciable concentrations’ of lead and arsenic were found in the workplace air.

No studies were identified addressing the chronic toxicity of arsine in humans.

## **7.2 Toxicity to Infants and Children**

No studies were identified allowing quantitative assessment of arsine toxicity in infants and children. Arsine’s mode of toxic action is not completely understood but appears to involve binding to erythrocyte sulfhydryl groups followed by intracellular ion loss and hemolysis (Rael et al., 2000). Clinical treatment of arsine poisoning usually involves exchange transfusion. It seems plausible that infants and children would be more sensitive to the irreversible hematotoxicity of arsine than adults due to their greater breathing rate per unit body weight.

## **7.3 Toxicity to Experimental Animals**

A number of studies were reviewed to understand the time-concentration relationship of arsine lethality. The most complete and relevant study was the IRDC (1985), which allowed determination of 1% and 5% lethality benchmark doses for exposure durations of 0.5 to 4 hours in rats. The most important acute non-lethal effects noted were hemolysis and reticulocytosis (Peterson and Bhattacharyya, 1985). Longer term effects of arsine also involved significant changes in hematological parameters (hemoglobin and mean corpuscular volume) (Blair, 1990).

LC<sub>50</sub> values reported by Gates (1946) are as follows: 120-210 ppm ( $380\text{-}670 \text{ mg}/\text{m}^3$ ) for 10 minutes in rats, 110 ppm ( $350 \text{ mg}/\text{m}^3$ ) for 30 minutes in dogs (equivalent to 190 ppm ( $610 \text{ mg}/\text{m}^3$ ) for 10 minutes), and 200-300 ppm ( $640\text{-}960 \text{ mg}/\text{m}^3$ ) for 10 minutes in rabbits. An LC<sub>50</sub> in mice was reported as 31 ppm ( $99 \text{ mg}/\text{m}^3$ ) for a 50-minute

exposure (Levvy, 1947). The survival time of the fatalities (4 days) was reported to be more or less independent of exposure concentration (2500 mg/m<sup>3</sup> to 25 mg/m<sup>3</sup>) and exposure duration.

The study by Levvy (1947) varied exposure durations for each given concentration of arsine. Because the mortality data were not presented in conventional form by the standard LC<sub>50</sub> method, the data were normalized to a 1-hour exposure using the modified form of Haber's equation (as described in Section 5.7.1 of the TSD):

$$C^n \times T = K,$$

where C = concentration, T = time, K = a constant determined at a given C, T and the exponent n is a constant determined experimentally. The exponent "n" of 1.8 was determined by varying the term n in a log-normal probit analysis (Crump and Howe, 1983; Crump, 1984) until the lowest chi-square value was achieved. Fifty-four data points were used to estimate the exponent n because these points were of sufficient duration ( $\geq 5$  minutes) and resulted in the best chi-square fit for the line and obvious heterogeneity (Table 7.3.1). This relationship indicates that the toxicity of arsine varies approximately with the product of the square of concentration times time rather than simply concentration times time.

**Table 7.3.1 Arsine Mortality in Mice: Results from Levvy (1947) and 1-Hour Adjusted Concentrations Using Haber's Equation ( $C^n \times T = K$ , where  $n = 1.8$ ).**

| Concentration (ppm) | Exposure Duration (min) | Mortality (no. died/total) | 1-Hour Adjusted Concentration (ppm) |
|---------------------|-------------------------|----------------------------|-------------------------------------|
| 157*                | 10                      | 30/30                      | 58                                  |
|                     | 5                       | 28/30                      | 39                                  |
|                     | 2.5                     | 17/30                      | 27                                  |
|                     | 1.7                     | 0/30                       | 22                                  |
| 78.4*               | 15                      | 21/30                      | 36                                  |
|                     | 9                       | 10/30                      | 27                                  |
| 31.4                | 70                      | 30/30                      | 34                                  |
|                     | 50                      | 15/30                      | 28                                  |

\* Shaded rows include data used for determination of the ED<sub>05</sub> and BD<sub>05</sub>

Craig and Frye (1988) reported a 4-hour LC<sub>50</sub> of 42.6 ppm in rats. However, when the rats were separated by sex for statistical purposes, there was slightly greater mortality among females than males (38.9 ppm LC<sub>50</sub> for females vs. 46.8 ppm LC<sub>50</sub> for males). No abnormalities were seen at necropsy except red discharge from nose, mouth, and genitalia at the higher concentrations. A concentration-related suppression of body weight gain was observed during the first week of the 14-day post-observation period.

The most comprehensive arsine lethality study was undertaken by IRDC (1985). LC<sub>50</sub>s of 240, 178, and 45 ppm were determined in rats (10 rats/sex/group) for 30 minute, 1 hour, and 4-hour exposures, respectively. Deaths generally occurred within 3 days



following 30-minute exposure to arsine. As in the previous study (Craig and Frye, 1988), there was slightly greater mortality in females than males. Adverse effects noted during exposure included dyspnea, while effects noted post-exposure included a concentration-related increase in hematuria, dark material around the head or the anogenital area, and pallor of ears, eyes, and feet. The higher concentrations resulted in weight loss immediately following exposure, suppressed weight gain during the first week and compensatory weight gains during the second week post-exposure. Necropsy on animals that died showed red, yellow or orange fluid in the bladder, stomach, or intestine, and discoloration of the kidneys, lungs, and liver.

Data in the IRDC (1985) report were used to determine the exponent “n” in the equation  $C^n \times T = K$ . This was done by varying the term n in a log-normal probit analysis (Crump, 1984; Crump and Howe, 1983) until the lowest chi-square value was achieved. The value of “n” for extrapolation to 1-hour exposure was dependent on exposure duration. For extrapolation from 30 minutes to 1-hour exposure,  $n = 2.2$ ; for extrapolation from 4-hours to 1-hour exposure,  $n = 1.0$ .

Table 7.3.2 contains the studies which provided adequate raw mortality data from which a maximum likelihood estimate corresponding to 5% lethality ( $ED_{05}$ ) and benchmark dose at the 95% lower confidence interval of the  $ED_{05}$  and  $ED_{01}$  ( $BD_{05}$  and  $BD_{01}$ , respectively) could be determined.

**Table 7.3.2 Animal Lethality Benchmark Dose Determinations in ppm for Arsine**

| Reference            | Species | Exposure Time (min) | $LC_{50}$<br>60 min <sup>1</sup> | $ED_{05}$<br>60 min <sup>1</sup> | $BD_{05}$<br>60 min <sup>1</sup> | $BD_{01}$<br>60 min <sup>1</sup> |
|----------------------|---------|---------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| IRDC, 1985           | rat     | 30                  | 175                              | 120                              | 105                              | 86                               |
|                      | rat     | 60                  | 178                              | 112                              | 88                               | 66                               |
|                      | rat     | 240                 | 181                              | 118                              | 101                              | 80                               |
| Craig and Frye, 1988 | rat     | 240                 | 170                              | 125                              | 102                              | 84                               |
| Levvy, 1947          | mice    | varied <sup>2</sup> | 29                               | 20                               | 16                               | 13                               |

<sup>1</sup> Exposure time was extrapolated to 60 minutes, if needed, using a modification of Haber’s equation ( $C^n \times T = K$ ). For rats,  $n = 2.2$  for extrapolation from 30 minutes to 1-hour, or  $n = 1.0$  for extrapolation from 4 hours to 1-hour; for mice,  $n = 1.8$ .

<sup>2</sup> Lethality data for 5 exposure durations were pooled and normalized to a 1-hour exposure using the equation  $C^n \times T = K$  (see Table 1).

In other experimental animal studies, a reduction in hematocrit as a function of arsine concentration was observed in mice following a 1-hour exposure (Peterson and Bhattacharyya, 1985). A LOAEL of 9 ppm (29 mg/m<sup>3</sup>) and a NOAEL of 5 ppm (16 mg/m<sup>3</sup>) were reported. The demarcation between the NOAEL and LOAEL for this non-lethal effect was well defined, not only among the exposure groups (5 ppm vs. 9 ppm), but also among individual mice in each exposure group (Peterson, 1990). Hematologic recovery of the surviving mice was gradual but nearly complete within 11 days after exposure (Peterson and Bhattacharyya, 1985). The study also reported a

NOAEL of 15 ppm (100% survival) and LOAEL of 26 ppm (100% lethality) for lethality.

A continuous benchmark dose analysis of these data was performed. The full data set on hematocrit reduction 24 hours after exposure gave a  $BMD_{05}$  of 7.81 ppm and a  $BMDL_{05}$  of 5.2 ppm (quadratic continuous model fit  $P = 0.16$ ). The only other data sets that were adequately fit were the 24 hour increase in reticulocyte count (%) with the 11 and 26 ppm outliers removed (power continuous model,  $P = 0.50$ ) and the 5 days values with the 9 ppm outlier removed (cubic continuous model,  $AIC = 61.8$ ). Several response levels were evaluated including 25% relative, 1 and 2 % absolute increases and 1 and 2 standard deviations. The latter SD levels were closest to the minimal significant increase levels and exceeded the control plus one control SD values of 0.88 ppm (24 hr) and 2.0 (5 days). For a 1 SD response level at 24 hours the  $BMD_{1SD} = 3.29$  ppm and the  $BMDL_{1SD} = 2.17$  ppm. The values for 2SD were  $BMD_{2SD} = 4.69$  ppm and  $BMDL_{2SD} = 3.50$  ppm. For the 5 days data set the  $BMD_{2SD} = 4.32$  ppm and the  $BMDL_{2SD} = 2.70$  ppm. Reticulocytosis may be a more sensitive indicator of adverse hematologic effects of arsine exposure than hematocrit reduction.

A subchronic study in male and female rats and female mice (Fowler et al., 1989) supports the sharp demarcation in dose-response noted by Peterson and Bhattacharyya (1985). All treatment groups exposed to arsine (6 hr/day, 5 days/week) at concentrations of 10 ppm and above showed 100 percent mortality within 4 days while those exposed to 5 ppm or less showed no mortality or overt signs of toxicity. Other effects observed included a dose-related increase in spleen weight and a slight increase in liver weight. Blood samples taken at necropsy showed a slight dose-related decrease in hematocrit and a marked dose-related increase in the activity of red blood cell ALAD ( $\delta$ -aminolevulinic acid dehydratase).

In a 90-day study, male and female mice were exposed to 0, 0.025, 0.5, and 2.5 ppm arsine gas for 6 hours/day, 5 days/week (Blair et al., 1990). After 5, 15, and 90 days, blood was collected for hematologic analysis. Exposure to 2.5 ppm had significant effects on all hematological parameters for nearly the entire exposure period, while 0.5 ppm caused only a few significant changes in hematological parameters at day 90 of exposure (decreased hemoglobin in males and increased MCV in females). Exposure to 0.025 ppm was without effect.

A continuous benchmark dose analysis was performed on the data sets of Blair et al. 1990. Adequate fits to the hematocrit data were obtained with the linear and quadratic models with  $BMDL_{025}$  (relative risk) values ranging from 0.128 to 0.894 ppm ( $P$  values for model fits of 0.11 to 0.96). Absolute reticulocyte count increases gave continuous  $BMDL_{10}$ 's ranging from 0.22 to 0.68 ppm with linear and quadratic models ( $P$  values of 0.31 to 0.99). However, due to the poor dose spacing, essentially a missing dose level between 0.025 and 0.5 ppm, these results are considered inconclusive in determining an alternative NOAEL to 0.025 ppm.

## 7.4 Developmental and Reproductive Toxicity

In an unpublished study, workers in one semiconductor plant were reported to have a 39% rate of miscarriage, almost twice the national average (Sanger, 1987). Workers were exposed to unidentified levels of arsine gas, but other possible exposures were not identified.

A developmental toxicity study exposed pregnant rats and mice to 0.025, 0.5, or 2.5 ppm (0.079, 1.5, or 7.9 mg/m<sup>3</sup>) arsine for 6 hours per day on gestation days 6 through 15 (Morrissey et al., 1990). The rats exposed to 2.5 ppm exhibited a significant increase in fetal body weight, but no other endpoints of developmental toxicity were observed. The incidence of malformations observed in arsine exposed mice at 0.025 ppm (exencephaly) and at 2.5 ppm (unfused eyelids) was not significantly different from control mice.

## 8. Derivation of Reference Exposure Levels

### 8.1 Acute Reference Exposure Level for Inorganic Arsenic

|  |  |
|--|--|
| <i>Study</i>                                     | Nagymajtenyi et al., 1985  |
| <i>Study population</i>                          | pregnant mice  |
| <i>Exposure method</i>                           | maternal inhalation exposure   |
| <i>Exposure continuity</i>                       |  |
| <i>Exposure duration</i>                         | 4 hours per day on gestation days 9, 10, 11, and 12                                    |
| <i>Critical effects</i>                          | decreased fetal weight   |
| <i>LOAEL</i>                                     | 0.26 mg/m <sup>3</sup> As <sub>2</sub> O <sub>3</sub> (0.197 mg As/m <sup>3</sup> )    |
| <i>NOAEL</i>                                     | not observed   |
| <i>Benchmark concentration</i>                   | not derived  |
| <i>Time-adjusted exposure</i>                    | n/a  |
| <i>Human Equivalent Concentration</i>            | n/a  |
| <i>LOAEL uncertainty factor (UF<sub>L</sub>)</i> | 10 (no NOAEL)  |
| <i>Subchronic uncertainty factor (UFs)</i>       | n/a  |
| <i>Interspecies Uncertainty Factor</i>           |  |
| <i>Toxicokinetic (UF<sub>A-k</sub>)</i>          | √10 (animal study)   |
| <i>Toxicodynamic (UF<sub>A-d</sub>)</i>          | √10 (animal study)   |
| <i>Intraspecies Uncertainty Factor</i>           |  |
| <i>Toxicokinetic (UF<sub>H-k</sub>)</i>          | √10 (remaining interindividual variation: study considered effects on fetus or infant) |
| <i>Toxicodynamic (UF<sub>H-d</sub>)</i>          | √10 (interindividual variation)  |
| <i>Cumulative uncertainty factor</i>             | 1,000  |
| <i>Reference Exposure Level</i>                  | <b>0.0002 mg As/m<sup>3</sup> (0.20 µg As/m<sup>3</sup>)</b>                           |

Acute Reference Exposure Levels are levels at which intermittent one-hour exposures are not expected to result in adverse health effects (see Section 5 in the Technical Support Document). The most appropriate study for the basis of an acute REL for arsenic is

Nagymajtenyi et al. (1985). This study was selected since it measured a sensitive toxicological endpoint with a relevant route of exposure, and the experimental design and reporting were considered adequate (as specified in the Non-cancer Risk Assessment technical support document, Section 4.1.1). It involved a significant number of animals exposed by inhalation to three dose levels plus a control. Unfortunately, no NOAEL was obtained. However, a significant dose-related reduction in fetal weight and increased incidences of intrauterine growth retardation, skeletal malformations, and hepatocellular chromosomal aberrations were observed in mice following maternal inhalation exposure to 200  $\mu\text{g As/m}^3$  (260  $\mu\text{g As}_2\text{O}_3/\text{m}^3$ ) for 4 hours on gestation days 9, 10, 11, and 12 ( $p < 0.05$ ). The most sensitive effect, decreased fetal weight, was observed at 200  $\mu\text{g As/m}^3$ , so 200  $\mu\text{g As/m}^3$  was taken as a LOAEL. Maternal toxicity data were not reported. This study is used as the basis of the acute REL:

$$0.2 \text{ mg/m}^3 / 1000 = 0.0002 \text{ mg/m}^3 = 0.2 \text{ } \mu\text{g As/m}^3 \text{ (equivalent to 0.065 ppb arsine gas)}$$

No temporal adjustment was made for the critical study since the critical period of exposure for a developmental effect may be very short relative to the study duration (OEHHA, 2007). The study concentration with appropriate uncertainty factors is a “not to exceed” value. An uncertainty factor of 10 ( $\text{UF}_L$ ) was used to account for the lack of a no observed adverse effect level (NOAEL). A second uncertainty factor of 10 was used to account for interspecies differences between the test species and humans. This factor is the product of two components addressing pharmacokinetic ( $\text{UF}_{A-k}$ ) and pharmacodynamic ( $\text{UF}_{A-d}$ ) differences, each assumed to be the  $\sqrt{10}$ . A final uncertainty factor of 10 was applied to address human interindividual differences in pharmacokinetics ( $\text{UF}_{H-k}$ ) and pharmacodynamics ( $\text{UF}_{H-d}$ ) also assumed to be  $\sqrt{10}$  each. The overall uncertainty of extrapolating from 4-hour exposures in mice (LOAEL) to no anticipated effects in humans is 1000 as noted in table above and the calculation of the acute REL. The rationale for the choice and value of uncertainty factors used by OEHHA is provided in the Non-cancer Risk Assessment technical support document (Section 4.4.3).

Inorganic arsenic (oxides) are listed as developmental toxicants under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). The studies reviewed in this document support the conclusion that exposure to inorganic arsenic may affect fetal weight, spontaneous abortion, neonatal death and postnatal neurological development.

In humans, the logarithm of infant mortality (death) increases linearly as birth weight decreases from 3500 to 1000 grams (Hogue et al., 1987; Rees and Hattis, 1994). This log-linear relationship exists on both sides of the weight (2500 g) conventionally used as a cutoff defining low birth weight. There is no evidence for a threshold. Thus any reduction in fetal weight is a cause for concern since it increases mortality. In the absence of certainty, OEHHA takes the health protective approach that the reduced weight effect in the animal fetuses may be biologically significant, particularly when viewed from a population perspective.

## 8.2 Inorganic Arsenic 8-Hour Reference Exposure Level

The 8-hour Reference Exposure Level is a concentration at or below which adverse noncancer health effects would not be anticipated for repeated 8-hour exposures which might include daily occupational, in-home or in-school exposures. (see Section 6 in the Technical Support Document).

Due to the possibility of repeated exposure and the relatively slow clearance of arsenic compounds, the 8-hour REL is taken to be equivalent to the chronic REL. The half-life of the initial exponential phase of excretion of arsenic after a single dose is typically between one and two days, but there are also several much slower excretion processes. So a single exposure to arsenic would take several days to be cleared, mainly via urinary metabolites. Repeated exposures can significantly prolong the clearance of arsenic as the internal dose accumulates, so that in terms of internal dosimetry it would be difficult to distinguish repeated periodic exposure from chronic exposure scenarios. An individual exposed daily via air and/or drinking water might show very similar urinary arsenic excretion to another individual exposed only periodically at work, school etc.

## 8.3 Inorganic Arsenic Chronic Reference Exposure Level

|  |  |
|--|--|
| <i>Study</i>                                     | Wasserman et al. (2004); Tsai et al. (2003)  |
| <i>Study population</i>                          | 201 children 10 years of age   |
| <i>Exposure method</i>                           | drinking water   |
| <i>Exposure continuity</i>                       | continuous   |
| <i>Exposure duration</i>                         | 9.5 to 10.5 years  |
| <i>Critical effects</i>                          | Decrease in intellectual function, adverse effects on neurobehavioral development                        |
| <i>LOAEL</i>                                     | 0.23 µg As/m <sup>3</sup> based on est. LOAEL of 2.27 µg/L (Wasserman et al., 2004; see Section 8.3.1.1) |
| <i>NOAEL</i>                                     | not observed   |
| <i>Benchmark concentration</i>                   | not derived  |
| <i>Time-adjusted exposure</i>                    | 117.8 µg As/L (0.094 to 790 µg As/L)   |
| <i>Human DAF concentration</i>                   |  |
| <i>LOAEL uncertainty factor (UF<sub>L</sub>)</i> | 3 (LOAEL estimated by quantitative analysis of study data)   |
| <i>Subchronic uncertainty factor (UFs)</i>       | 1 (default: duration >8% of lifetime)  |
| <i>Interspecies uncertainty factor</i>           |  |
| <i>Toxicokinetic (UF<sub>A-k</sub>)</i>          | 1 (default: human study)   |
| <i>Toxicodynamic (UF<sub>A-d</sub>)</i>          | 1 (default: human study)   |
| <i>Intraspecies uncertainty factor</i>           |  |
| <i>Toxicokinetic (UF<sub>H-k</sub>)</i>          | √10 (remaining interindividual variation: study considered effects on 10 year-old but not infant)        |
| <i>Toxicodynamic (UF<sub>H-d</sub>)</i>          | √10 (default, interindividual variation)   |
| <i>Cumulative uncertainty factor</i>             | 30   |
| <i>Inhalation Reference Exposure Level</i>       | <b>0.015 µg As/m<sup>3</sup></b>   |
| <i>Oral Reference Exposure Level</i>             | 0.0035 µg/kg-d   |

The chronic Reference Exposure Level is a concentration at which adverse noncancer health effects would not be expected from chronic exposures (see Section 7 in the Technical Support Document).

### 8.3.1 Review and Analysis of Studies Supporting a Chronic REL

#### 8.3.1.1 Child Based Values

A number of studies have indicated potentially greater toxicity of arsenic exposure during childhood (see below). Although some PBPK modeling has been applied to inorganic arsenic and its methyl metabolites, the modes of toxic action and relevant internal dosimetry are not sufficiently understood at present to use this modeling directly in REL development. In this section we compare quantitative analyses of dose-responses and LOAELs in key studies involving arsenic exposures in children. Health protective exposure levels derived from these analyses will be compared with similar analyses from studies in adults in the following section.

The study of Wasserman *et al.* (2004) indicated a dose-response of decreasing Full-Scale intellectual function raw scores with increasing drinking water arsenic exposure in 10-year olds. The values in their Fig.2 give an exact fit to a quadratic model ( $Y = Y_0 + aX + bX^2$ ;  $Y_0$  intercept = 0,  $a = -0.443$ ,  $b = 0.0063$ ,  $R^2 = 1.0$ ) with a low dose slope of  $-0.44$  points/ $\mu\text{g/L}$ . Assuming an adverse effect level of one point loss, then the corresponding arsenic concentration can be calculated as:

$$-1\text{point}/-0.44\text{ point}/\mu\text{g/L} = 2.27\ \mu\text{g/L}.$$

This level might be equivalent to a LOAEL. Further, assuming water intake of 1 Liter/day (L/d) and essentially complete intestinal absorption, this can be converted to an intake of  $2.3\ \mu\text{g/d}$ . If we assume a drinking water intake based on the 95% upper confidence level (UCL) for U.S. children aged 1 to 10 years of  $1564\ \text{mL/day}$  the intake would be somewhat higher at  $3.6\ \mu\text{g/d}$  (OEHHA, 2000; Table 8.3). Since 10-year old males would inhale about  $9.9\ \text{m}^3/\text{d}$  (OEHHA, 2000), if airborne arsenic were 100% absorbed, this oral effect level would be equivalent to an inhalation level of  $2.3\ \mu\text{g/day}/9.9\ \text{m}^3/\text{day} = 0.23\ \mu\text{g}/\text{m}^3$ . Assuming a more realistic inhalation absorption of 50% would give a value of  $0.46\ \mu\text{g}/\text{m}^3$ . Applying a 3-fold UF for an estimated LOAEL based on a quantitative dose response analysis (a higher value would be used without a dose response analysis) and 10-fold for inter-individual variation since only 10-year olds were studied, a health protective air concentration of  $0.015\ \mu\text{g}/\text{m}^3$  can be calculated. An oral value based on the average study body weight of  $21.9\ \text{kg}$  and 100% oral absorption would be  $2.3\ \mu\text{g/d}/21.9\ \text{kg} = 0.105\ \mu\text{g}/\text{kg-day}$ . Applying the same overall uncertainty factor of 30 the oral health protective value would be  $0.105\ \mu\text{g}/\text{kg-day}/30 = 0.0035\ \mu\text{g}/\text{kg-day}$ .

The data of Tsai *et al.* (2003) for 13 year old children gave dose response relationships for arsenic exposure metrics of ppb As in drinking water and cumulative arsenic intake (mg) vs. the pattern memory (PM) and switching attention (SA) endpoints (ms). A continuous benchmark response analysis for ppb As vs. ms test duration was conducted

for PM ( $BMD_{05} = 49.75$ ;  $BMDL_{05} = 31.2$  ppb) and SA ( $BMD_{05} = 28.81$ ;  $BMDL_{05} = 19.73$  ppb) both using a linear model. For cumulative As intake the PM endpoint data were similarly fit by a linear model ( $BMD_{05} = 194.1$ ;  $BMDL_{05} = 122.7$  mg) and the SA data by a polynomial (quadratic) model ( $BMD_{05} = 39.1$ ;  $BMDL_{05} = 25.4$  mg; see Fig. 1). The SA endpoint appears to be the most sensitive. Based on the SA  $BMDL_{05}$  of 19.7 ppb and 1 L/d drinking water intake a minimum effect level of 19.7  $\mu\text{g/d}$  is estimated. If we assume a drinking water intake, based on the 95% UCL for U.S. children aged 11 to 19 years of 2.143 L/d the intake would be 2-fold higher at 42.2  $\mu\text{g/day}$  (OEHHA, 2000; Table 8.3). Using uncertainty factors of 10 for interindividual variation and 3 for extrapolation from a minimum to a no effect level, a health protective intake of  $19.7 \mu\text{g/d}/30 = 0.658 \mu\text{g/d}$  is calculated. Assuming inhalation of  $10 \text{ m}^3/\text{d}$  and 50 % absorption (default) this value can be converted to an inhalation value of  $0.658 \mu\text{g/day}/(0.50 \times 10 \text{ m}^3/\text{day}) = 1.32 \mu\text{g}/\text{m}^3$ . Using the SA cumulative  $BMDL_{05}$  of 25.4 mg As and 10 years exposure, an effect level of  $25.4 \text{ mg}/(10 \text{ yr} \times 365 \text{ days/yr}) = 6.96 \mu\text{g/day}$  is calculated. Using the same assumptions and UFs as above, an inhalation value of  $0.044 \mu\text{g}/\text{m}^3$  can be derived based on As concentration. The cumulative dose metric is a more accurate estimate of arsenic exposure than As water concentration, so the value of  $0.046 \mu\text{g}/\text{m}^3$  or  $0.05 \mu\text{g}/\text{m}^3$  (rounded) is preferred over the concentration based value. An oral value based on an average body weight for a 13-14 year old child (OEHHA, 2000) of 50 kg is  $6.96 \mu\text{g/day}/50 \text{ kg} = 0.139 \mu\text{g}/\text{kg-d}$ . Applying the same overall uncertainty factor of 30 would give  $0.139 \mu\text{g}/\text{kg-day}/30 = 0.0046 \mu\text{g}/\text{kg-day}$ .

The quantal responses for skin lesions in young children ( $\leq 9$  yr) and adolescents (10-19 yr) from Mazumder et al. (1998) were subjected to benchmark dose analysis. For young children, the quantal linear model adequately fit the data ( $X^2 = 6.1$ ,  $P = 0.30$ ) with a  $BMD_{01} = 54.4 \mu\text{g/L}$  and a  $BMDL_{01} = 39.3 \mu\text{g/L}$ . For adolescents, the best fitting model was the log probit ( $X^2 = 0.77$ ,  $P = 0.68$ ) with a  $BMD_{01} = 77.3 \mu\text{g/L}$  and a  $BMDL_{01} = 47.4 \mu\text{g/L}$ . These values are similar to the analysis of all age groups combined (above) and application of a 10-fold UF for intraspecies variation seems adequate for these data. Thus the health protective intake for children for skin effects would be in the range of 3.9 to 4.7  $\mu\text{g/d}$  for one Liter/day water intake. For conversion to inhalation equivalent, young children are assumed to inhale  $9.9 \text{ m}^3/\text{day}$  and adolescents  $14 \text{ m}^3/\text{day}$  (OEHHA, 2000). It is further assumed that 50 percent of inhaled arsenic is absorbed via the pulmonary and gastro-intestinal routes. The resulting health protective values would be 0.68 to  $0.79 \mu\text{g}/\text{m}^3$ .

A study in Thailand (Siripitayakunkit et al., 1999) related drinking water arsenic exposure, indicated by hair arsenic, to IQ in 529 six to nine year old children. A continuous benchmark dose response analysis of this data set gave a  $BMD_{05} = 0.035 \mu\text{g As/g hair}$  and  $BMDL_{05} = 0.0155 \mu\text{g As/g}$  (polynomial model). A slope of  $-3.2 \text{ IQ points}/\mu\text{g/g}$  was derived from the  $BMDL_{05}$ . Using the conversion factor of  $0.01 \mu\text{g As/g hair}/\mu\text{g As/Liter of water}$  (Kurtio et al. 1998), a decrease of 1 IQ point would be equivalent to chronic consumption of  $30 \mu\text{g As/L water}$  (OEHHA, 2004). At one liter/day water consumption the  $30 \mu\text{g/d}$  value is over an order of magnitude higher than the analogous estimate indicated by the Wasserman et al. (2004) study above. An

inhalation value was derived as above:  $30 \mu\text{g/day}/(10 \text{ m}^3/\text{day} \times 0.50 \times 30\text{UF}) = 0.20 \mu\text{g/m}^3$ .

The visual perception data from Siripitayakunkit et al. (2001) was subjected to continuous benchmark dose analysis. The BMDL<sub>035</sub> of 2.40  $\mu\text{g/g}$  hair (polynomial model) was near the low level mean minus one SD score (20.5), presumably an adverse effect level on visual perception as defined by the authors. The linear model gave a higher value (3.69  $\mu\text{g/g}$ ) but did not fit the data as well in the low exposure range. Using the conversion factor above, one liter per day water consumption, and a 30-fold cumulative UF results in a presumptive health protective intake of 8  $\mu\text{g/d}$  for this endpoint ( $2.40 \mu\text{g/g} \div 0.01 \mu\text{g/g}/\mu\text{g/Liter} \times 1 \text{ Liter/day} \div 30\text{UF} = 8.00 \mu\text{g/d}$ ). An inhalation value was derived as above:  $8.0 \mu\text{g/day}/(10 \text{ m}^3/\text{day} \times 0.50) = 1.6 \mu\text{g/m}^3$ .

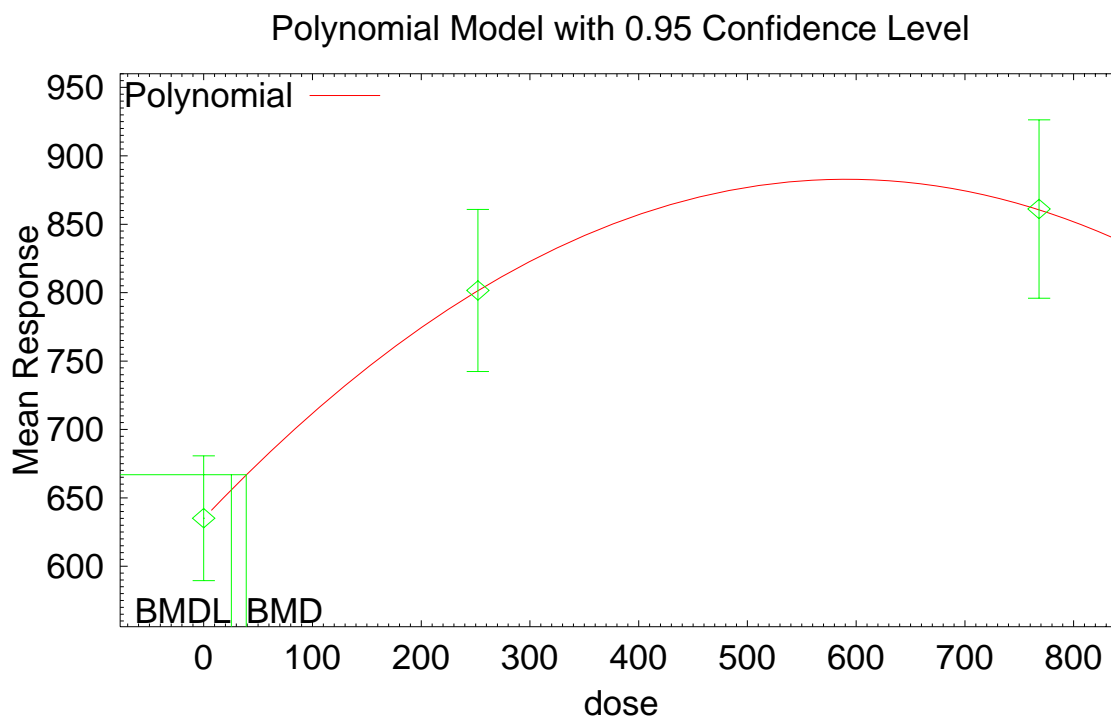
Chronic arsenic exposure appears to have adverse effects on intellectual development and visual perception in children. While the quantitation of these effects and the toxicological significance of the criteria selected are somewhat uncertain, OEHHA thinks they are sufficient to support a cREL. It is uncertain whether neurological effects are the most sensitive caused by chronic arsenic exposure in children. Additional studies in exposed children are needed to adequately quantify adverse effects. The values above are summarized in Table 8.3.1. The child-based values range from 0.015 to 1.6  $\mu\text{g/m}^3$ . The geometric mean of the three cognitive endpoint values is 0.053  $\mu\text{g/m}^3$ .

**Table 8.3.1. Inhalation Values Derived from Human Child Studies**

| Study                          | Toxic Endpoint          | Criterion         | Value                            | Derived cREL, $\mu\text{g/m}^3$ |
|--------------------------------|-------------------------|-------------------|----------------------------------|---------------------------------|
| Wasserman et al. (2004)        | Intellectual function   | One point loss    | 2.27 $\mu\text{g/d}$             | 0.015                           |
| Siripitayakunkit et al. (1999) | IQ                      | One point loss    | -3.2 IQ/ $\mu\text{g/g}$ hair As | 0.20                            |
| Siripitayakunkit et al. (2001) | Visual perception loss  | LOAEL             | 240 $\mu\text{g/d}$              | 1.6                             |
| Mazumder et al. (1998)         | Skin Lesions            | LED <sub>01</sub> | 39-47 $\mu\text{g/d}$            | 0.68-0.79                       |
| Tsai et al. (2003)             | Neurobehavioral effects | LED <sub>05</sub> | 7 $\mu\text{g/d}$                | 0.05                            |



**Figure 8.3.1 Switching attention (ms) in 13-year old children versus cumulative arsenic intake in mg (Tsai et al., 2003).**



Inorganic arsenic is apparently more potent in its neurotoxic effects in humans than in experimental animals. The values of 2.27  $\mu\text{g}/\text{day}$  in Wasserman *et al* (2004) and 7  $\mu\text{g}/\text{day}$  in Tsai *et al* (2003) for cognitive effects in 10-13 year-old children are much lower than brain effects seen in animals e.g., 5 mg/kg-day in rats (Nagaraja and Desiraju, 1993; 1994) and 3.7 mg/kg-day in Rhesus monkeys (Heywood and Sortwell, 1979).

#### 8.3.1.2 Adult Based Values

In this section we review toxicological criteria from studies in adults that may serve as the basis for a chronic REL for inorganic arsenic or otherwise provide supporting information.

Studies in experimental animals show that inhalation exposure to arsenic compounds can produce immunological suppression, developmental defects, and histological or biochemical effects on the nervous system and lung, thus providing supportive evidence of the types of toxicity observed in humans. Among the inhalation studies, the lowest adverse effect level (LOAEL) was quite consistent:

- 245  $\mu\text{g As}/\text{m}^3$  for decreased bactericidal activity in mice (Aranyi et al., 1985);
- 200  $\mu\text{g As}/\text{m}^3$  for decreased fetal weight in mice (Nagymajtenyi et al., 1985); and
- 270  $\mu\text{g As}/\text{m}^3$  for decreased sperm motility in rats (Kamil'dzhanov, 1982).

Reports of human inhalation exposure to arsenic compounds, primarily epidemiological studies of smelter workers, indicate that adverse health effects occur as a result of chronic exposure. Among the targets of arsenic toxicity are the respiratory system (Lundgren, 1954), the circulatory system (Lagerkvist et al., 1986), the skin (Perry et al., 1948), the nervous system (Blom et al., 1985), and the reproductive system (Nordstrom et al., 1979). Occupational exposure levels associated with these effects ranged from 50 to 7000  $\mu\text{g As}/\text{m}^3$ . These epidemiological studies suffer, however, from confounding as a result of potential exposure to other compounds, which limits their usefulness in the development of the chronic REL.

A single study showed effects occurring at 4.9  $\mu\text{g As}_2\text{O}_3/\text{m}^3$  (Rozenstein, 1970). However, lack of detail with respect to endpoints and experimental design limits this study's usefulness for developing a Reference Exposure Level.

The cerebrovascular disease (CVD) and cerebrovascular infarct (CI) data of Chiou et al. (1997b) were subjected to benchmark dose analysis (BMD). The data were best fit using the quantal linear regression (QL) dose-response equation. Since the responses were of the order of 0.1 to 2 percent, the values calculated were for the 1 percent response ( $\text{ED}_{01}$ ) and its 95% lower confidence limit ( $\text{LED}_{01}$ ), rather than the usual 5 percent response values for the analysis of animal study data.

The values for CI were marginally better fit by the dose-response equation than those for CVD. Also the QL models gave better fits to the unadjusted data sets for both endpoints. The unadjusted  $\text{ED}_{01}$  and  $\text{LED}_{01}$  values with goodness of fit P value meeting the acceptable fit criterion of  $P \geq 0.1$  were 359 and 189  $\mu\text{g}/\text{L}$  for CVD and 268 and 166  $\mu\text{g}/\text{L}$  for CI, respectively. Using the cumulative dose metric these values were 5.1, 3.0, 5.9, and 3.5 (mg/L)-yr, respectively. Due to the severity of these and other endpoints analyzed below, the uncertainty in the dose assignments (range mid-points instead of averages), and the fact that the chosen points of departure or LEDs were generally two-fold or more above concurrent control levels, the  $\text{LED}_{01}$  should be considered equivalent to a LOAEL for the purposes of risk assessment. Due to the severity of the CI endpoint, a 100 UF was used to derive a health protective water concentration of 0.1 to 0.3  $\mu\text{g}/\text{L}$  based on the two dose metrics. For CVD with a 30 UF the corresponding values were 0.28 to 1.3  $\mu\text{g}/\text{L}$  (for details of analysis see OEHHA, 2004). Assuming 20  $\text{m}^3/\text{day}$  inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption, the corresponding inhalation values for these vascular effects would be for CI 0.10 to 0.33  $\mu\text{g}/\text{m}^3$  and for CVD 0.28 to 1.26  $\mu\text{g}/\text{m}^3$ .

BMD analysis of the ISHD data from Chen et al. (1996) showed that these data were well fit by the QL dose-response equation ( $\text{ED}_{01} = 8.27$  (mg/L)-yr,  $X^2 = 0.26$ ,  $P = 0.88$ ). The  $\text{LED}_{01}$  of 5.53 (mg/L)-yr should be considered an effect level for this endpoint. In this analysis the cumulative arsenic dose metric of (mg/L)-yr and resultant benchmark doses were divided by 70 yr to yield comparable lifetime drinking water concentrations of arsenic. Using a cumulative uncertainty factor of 100, a health protective concentration of 0.16  $\mu\text{g}/\text{L}$  can be derived (OEHHA, 2004). Assuming 20  $\text{m}^3/\text{day}$  inhalation, 2 Liters/day

water consumption and 50 percent inhalation absorption the corresponding health protective inhalation value for ISHD would be  $0.16 \mu\text{g}/\text{m}^3$ .

The Chen *et al.* (1995) data on the association of hypertension (HT) and cumulative arsenic intake via drinking water were subjected to BMD analysis. The QL dose-response equation fit the unadjusted data well but was somewhat less than adequate for the adjusted prevalence values. The acceptable criterion for the  $X^2$  goodness of fit test for the benchmark dose is  $P \geq 0.10$ . In the case of arsenic induced hypertension, the 10 percent effect level was chosen due to the higher background and greater dose response range. For HT the  $\text{LED}_{10}$  is considered an appropriate LOAEL for risk assessment. In the case of the adjusted data set, removal of the highest cumulative dose allows an acceptable fit of the QL equation with an  $\text{LED}_{10}$  of  $7.4 (\text{mg}/\text{L})\text{-yr}$ . The data of Rahman *et al.* (1999) were also analyzed. Both crude and adjusted data sets were well fit by the QL model with P values much greater than 0.1. The unadjusted  $\text{LED}_{10}$  value of  $6.3 (\text{mg}/\text{L})\text{-yr}$  from Bangladesh is quite similar to comparable value of  $7.2 (\text{mg}/\text{L})\text{-yr}$  from the Taiwan study (OEHHA, 2004). Health protective drinking water concentrations with a cumulative uncertainty factor of 30 ranged from  $0.55$  to  $0.68 \mu\text{g}/\text{Liter}$ . Assuming  $20 \text{ m}^3/\text{day}$  inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption the corresponding health protective inhalation value for HT would be  $0.55$  to  $0.70 \mu\text{g}/\text{m}^3$ .

The data of Chen *et al.* (2006) indicate a supralinear dose-response. The data were analyzed for benchmark response using metrics of time weighted average (TWA) and cumulative arsenic exposure of TWA times years of exposure or  $(\text{mg}/\text{L})\text{-yr}$ . Systolic hypertension quantal responses of the first four quintiles of the overall population ( $N = 8726$ ) were fit by the log-logistic model of BMDS (v 1.4.1). The  $\text{BMDL}_1$  values (1% response) of  $71.5 \mu\text{g}/\text{L}$  and  $0.66 (\text{mg}/\text{L})\text{-yr}$  were obtained ( $X^2 = 3.8$ ,  $P = 0.15$ ,  $\text{d.f.} = 2$ ). The pulse hypertension data were similarly fit using the longer-term exposure subpopulation ( $N = 6319$ ). In this case the 10% response level was used for  $\text{BMDL}_{10}$ 's of  $0.49 \mu\text{g}/\text{L}$  and  $0.004 (\text{mg}/\text{L})\text{-yr}$  ( $X^2 = 4.45$ ,  $P = 0.11$ ,  $\text{d.f.} = 2$ ). TWA  $\text{BMDL}$ s for systolic and pulse hypertension in arsenic exposed subpopulations with lower intakes of B vitamins were also evaluated. The  $\text{BMDL}_{10}$  values for populations with low dietary folate ranged from 62 to  $405 \mu\text{g}/\text{L}$  TWA. The results indicate a higher sensitivity of the pulse hypertension effect to low level arsenic than the systolic hypertension effect. The supralinearity of dose-response makes comparison with earlier studies problematic. For example, projected  $10^{-4}$  extra risk levels for pulse and systolic hypertension from this study are at least an order of magnitude less than values seen earlier with Chen *et al.* (1995) or Rahman *et al.* (1999) although cumulative arsenic exposures were 5-10 times higher in the latter studies (Table 6).

Similarly, the diabetes mellitus (DM) data of Lai *et al.* (1994) and Rahman *et al.* (1998) were analyzed. In this case, the QL dose-response model adequately fit both unadjusted and multivariate-adjusted prevalences. EDs and LEDs were determined for the 1 and 5 percent response levels. The  $\text{LED}_{05}$  for the adjusted values appear the best choice for a chronic criterion for arsenic-induced diabetes mellitus, i.e.,  $8.8 (\text{mg}/\text{L})\text{-yr}$  from Lai *et al.* and  $0.21 \text{ mg}/\text{L}$  from Rahman *et al.* The health protective drinking water derived from these values with a cumulative UF of 30 were  $0.84$  and  $1.4 \mu\text{g}/\text{L}$ , respectively (OEHHA,

2004). Assuming 20 m<sup>3</sup>/day inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption, the corresponding health protective inhalation values for diabetes mellitus would be 0.85 to 1.4 µg/m<sup>3</sup>.

In addition to the values noted above, an estimated LOAEL of 20 (mg/L)-yr for peripheral vascular disease from Tseng et al. (1996) was also included in this analysis. Using a cumulative UF of 30, a drinking water value of 1.9 µg/L was derived (OEHHA, 2004). Assuming 20 m<sup>3</sup>/day inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption, the corresponding health protective inhalation value for peripheral vascular disease would be 1.9 µg/m<sup>3</sup>. The study of Wang et al. (2002) on arsenic induced carotid atherosclerosis (subclinical) also gave an estimated LOAEL of 20 (mg/L)-yr and would yield the same health protective values.

The arsenic-induced skin keratosis and hyperpigmentation data of Mazumder et al. (1998) were analyzed as above (OEHHA, 2004). For both male and female skin keratosis data sets, adequate fits were obtained by the QL model with lower bound values (LED<sub>01</sub>) of 49.6 µg/L for males and 124 µg/L for females. Adequate fits could not be obtained for both hyperpigmentation data sets with the models available in the benchmark dose program; however, the dose-response graphs appeared to be linear in the lower exposure groups with respective LED<sub>01</sub>s of 18.9 and 34.7 µg/L. It appears that a single dose level outlier (125 µg/L) was largely responsible for the failure of the statistical test. Mazumder also included an assessment of skin keratosis and hyperpigmentation prevalence by dose per body weight. Using the dose metric of µg/kg-day, the skin hyperpigmentation data were still unable to be fit by the BMDS models. Therefore only the skin keratosis endpoint appears suitable for the development of a health protective value for arsenic-induced noncancer effects. Using a cumulative UF of 30, a drinking water value of 1.7 µg/L was derived. Assuming 20 m<sup>3</sup>/day inhalation, 2 Liters/day water consumption and 50 percent inhalation absorption, the corresponding health protective inhalation value for skin keratosis would be 0.34 µg/m<sup>3</sup>.

The skin lesion data of Rahman *et al.* (2006) was analyzed for benchmark response. The unadjusted data reported in Rahman's Table 3 was used with the mid points of the exposure concentration ranges (e.g, 5, 30, 100, 224, 450 µg/L) and the mean As exposures in Rahman's Table 4 (e.g., 9.8, 59.3, 127, 199, 344 µg/L). For the unadjusted male data, no adequate fit could be obtained. The female data was adequately fit by the quantal linear (P = 0.43) and log-logistic (P = 0.51) models. The latter giving a BMDL<sub>10</sub> of 6.28 µg/L with mid-point based exposure estimates, and the former giving a BMDL<sub>10</sub> of 108.2 µg/L with mean As concentrations. Similarly, for the cumulative As dose metric of (mg/L)-yr no adequate fit was obtained with the male data, while the female data were best fit by the log-probit model (P = 0.86) for a BMDL<sub>10</sub> of 2.80 (mg/L)-yr. Using the age and asset adjusted data with the average As concentrations, an adequate fit to the male data could be obtained with the multistage model if the top dose group was removed, BMDL<sub>10</sub> = 96.0 µg/L (X<sup>2</sup> = 0.60, P = 0.74). The female adjusted data set gave a lower BMDL of 65.4 µg/L despite the authors' finding that the males were more sensitive. This may simply reflect the difficulty of fitting the male data. In almost all

cases, the BMDL values are lower (indicating higher risk) than seen in the earlier study by Mazumder *et al.* (1998) analyzed above.

The inhalation values derived from oral human exposure studies above are summarized in Table 8.3.2. With the exception of the very low value derived from the pulse hypertension endpoint, the derived health protective inhalation values range over approximately one order of magnitude from 0.16 to 1.7  $\mu\text{g}/\text{m}^3$ . These adult values exceed the child-based values (range 0.015 to 1.6  $\mu\text{g}/\text{m}^3$ ). Therefore the proposed chronic REL value of 0.015  $\mu\text{g}/\text{m}^3$  is derived from the child arsenic exposure studies evaluated above and the adult studies provide supporting information.

**Table 8.3.2 Inhalation Values Derived from Adult Human Drinking Water Studies**

| Study                  | Toxic Endpoint                         | Criterion                                      | Value  | Derived chronic REL, ( $\mu\text{g}/\text{m}^3$ ) |
|------------------------|--|--|--|---|
| Chiou et al. (1997b)   | Cerebrovascular disease                | LED <sub>01</sub>                              | 378 $\mu\text{g}/\text{d}$                                 | 1.26  |
| Chiou et al. (1997b)   | Cerebrovascular infarct                | LED <sub>01</sub>                              | 332 $\mu\text{g}/\text{d}$                                 | 0.33  |
| Chen et al. (1996a)    | Ischemic Heart Disease Mortality       | LED <sub>01</sub>                              | 5.53 (mg/L)-yr   | 0.16  |
| Chen et al. (1995)     | Hypertension                           | LED <sub>10</sub>                              | 5.8 (mg/L)-yr  | 0.55  |
| Chen et al. (2006)     | Systolic and pulse hypertension        | SHT LED <sub>01</sub><br>PHT LED <sub>10</sub> | 71.5 $\mu\text{g}/\text{L}$<br>0.49 $\mu\text{g}/\text{L}$ | 1.43<br>0.0033                                    |
| Lai et al. (1994)      | Diabetes mellitus                      | LED <sub>05</sub>                              | 8.8 (mg/L)-yr  | 0.85  |
| Rahman et al. (1998)   | Diabetes mellitus                      | LED <sub>05</sub>                              | 0.21 mg/L  | 1.4   |
| Mazumder et al. (1998) | Skin keratosis                         | LED <sub>01</sub>                              | 50 $\mu\text{g}/\text{L}$                                  | 0.33  |
| Rahman et al. (2006)   | Skin keratosis or altered pigmentation | LED <sub>10</sub>                              | 65.4 $\mu\text{g}/\text{L}$                                | 0.44  |
| Tseng et al. (1996)    | Peripheral vascular disease            | est. LOAEL                                     | 20 (mg/L)-yr   | 1.69  |
| Wang et al. (2002)     | Carotid atherosclerosis                | est. LOAEL                                     | 20 (mg/L)-yr   | 1.69  |

In addition to being inhaled, airborne arsenic can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level for arsenic of 0.0035  $\mu\text{g}/\text{kg}\text{-day}$  is also proposed.

## 9. Arsine Based Calculations

The NAC/NRC (National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances/National Research Council Subcommittee on Acute Exposure Guideline Levels) derived an Acute Exposure Guidance Level-2 (AEGL-2, disabling) of 0.17 ppm ( $500 \mu\text{g}/\text{m}^3$ ) for one-hour exposure to arsine based on the hemolysis mouse data of Peterson and Bhattacharyya (1985) (Thomas and Young, 2001). Due to the steepness of the dose response the derivation of an AEGL-1 (Non-disabling) was considered inappropriate. Also the reliance on animal data was considered more “scientifically valid than AEGLs estimated from limited anecdotal human data”. The panel used a total UF of 30 (10 for interspecies differences and 3 for intraspecies differences).

Based on the same study data, OEHHHA calculated a continuous  $\text{BMDL}_{1SD}$  of 2.17 ppm ( $6.9 \text{ mg}/\text{m}^3$ ) for reticulocytosis. When this value was adjusted with uncertainty factors of 10 for interspecies and 30 for intraspecies differences (including 10 for the intraspecies toxicokinetic sub-factor, as proposed in OEHHHA, 2007 draft) the potential aREL for a one hour exposure was  $2.17 \text{ ppm}/300 = 0.0072 \text{ ppm}$  ( $23 \mu\text{g}/\text{m}^3$ ).

Despite the additional 10-fold margin of safety and more sensitive endpoint incorporated in the OEHHHA derivation summarized above, there is still residual uncertainty in this comparison aREL value for arsine. There is particular concern with respect to the lack of adequate human data, given that rodents appear more resistant to the effects of acute exposure to various inorganic forms of arsenic than humans. The analogy between arsine and other inorganic forms of arsenic is supported by the observation that arsine exposure in humans and experimental animals results in similar metabolites excreted in urine as result from other inorganic arsenic exposure (Landrigan et al., 1982; Buchet et al., 1998). A further source of concern with a REL based on the Peterson and Bhattacharyya (1985) study is that while the margin of exposure for hemolysis is greater than 1000, the margin for total lethality is less than 4000. Although a steep dose-response slope for acute lethality is not unprecedented, it is a problematic feature when combined with the uncertainty in animal-to human extrapolation noted above. Thus, OEHHHA staff have low confidence in using the Peterson and Bhattacharyya study as a basis of an aREL value for arsine and instead will rely on the aREL based on arsenic trioxide inhalation in mice ( $0.2 \mu\text{g}/\text{m}^3$  arsenic, equivalent to 0.065 ppb arsine), which is sufficiently protective for all inorganic arsenic species.

A comparison of various possible values for an 8-hour REL for arsine is shown in Table 8.3.3. Adjustment of the one-hour NOAEL from Peterson and Bhattacharyya (1985) to eight hours using the modified Haber equation for mice gives a value of 1.6 ppm ( $4.98 \text{ mg}/\text{m}^3$ )/300UF = 0.053 ppm ( $17 \mu\text{g}/\text{m}^3$ ). This value is much higher than the values observed by Williams et al. (1981) in workers exposed to arsine concentrations estimated at 0.01 to 0.07  $\text{mg}/\text{m}^3$ . The adverse effects noted included headache, nausea, weakness and vomiting. Although based on only a couple of subjects, the Williams et al. study

would indicate an 8-hour value of about  $0.04 \text{ mg/m}^3 / 30 \text{ UF} = 0.001 \text{ mg/m}^3$  or  $1 \mu\text{g/m}^3$ . Alternatively, the 90-day study of Blair *et al.* (1990) gives a NOAEL for hematologic effects in mice of 0.025 ppm arsine at 6 hours/day, 5 days/week. Applying the same 300 UF as above gives 0.083 ppb or  $0.26 \mu\text{g/m}^3$ . This latter figure seems more in line with the limited human observations and more suitable for potentially repeated 8-hour exposures to arsine. The intraspecies extrapolation includes additional uncertainty factors (PK + PD UF) for exposure of infants and children to arsine.

**Table 8.3.3. Development of Health Protective Values for Arsine**

| Study                            | Toxic Endpoint  | NOAEL/LOAEL/<br>BMDL  | Derived REL<br>$\mu\text{g/m}^3$ |
|----------------------------------|---|---|----------------------------------|
| Peterson and Bhattacharyya, 1985 | Reticulocytosis in mice 1 hour exposure                     | BMDL <sub>1SD</sub><br>2.17 ppm<br>6.9 $\text{mg/m}^3$                | Acute<br>23                      |
| Peterson and Bhattacharyya, 1985 | As above with 8-hour adjustment                             | 1.6 ppm<br>4.98 $\text{mg/m}^3$                                       | 8-hour<br>17                     |
| Williams <i>et al.</i> , 1981    | Headache, nausea, weakness, and vomiting in exposed workers | 0.01 to 0.07 $\text{mg/m}^3$ ,<br>average 0.04 $\text{mg/m}^3$ LOAEL. | 8-hour<br>1.0                    |
| Blair <i>et al.</i> , 1990       | Hematologic effects   | NOAEL<br>0.025 ppm 6 hr/day   | 8-hour<br>0.26                   |

PBPK modeling of arsenic species in experimental animals and humans is presently considered inadequate to apply directly to the derivation of RELs for repeated arsine exposures.

Arsine exposure at atmospheric concentrations that caused adverse maternal effects did not adversely affect endpoints of developmental toxicity in mice or rats (Morrissey *et al.*, 1990). In the absence of neurodevelopmental studies with arsine, it is assumed that such an effect would be comparable to those of other inorganic forms of arsenic. In view of the observed effect levels for hematological effects noted in the animal studies, both 8 hour and chronic effects of arsine are considered to be adequately covered by the respective cREL for inorganic arsenic based on neurodevelopmental effects observed in children (i.e.,  $0.015 \mu\text{g/m}^3$  arsenic, equivalent to 0.005 ppb arsine)). In view of the concern over neurodevelopmental effects for all inorganic forms of arsenic, OEHHA concludes that it is appropriate to apply this value for 8-hour and chronic exposures to arsine.

## **10. Arsenic as a Toxic Air Contaminant that Disproportionately Impacts Children**

In view of the neurodevelopmental toxicity studies discussed above, it is clear that infants and children are more susceptible to the toxicity of arsenic than adults. OEHHA recommends that inorganic arsenic and arsine be identified as a Toxic Air Contaminant

the disproportionately impacts children under the California Health and Safety Code Section 39699.5.



## 11. References

ACGIH (1992). Documentation of the threshold limit values and biological exposure indices. Cincinnati (OH): American Conference of Government Industrial Hygienists, Inc.

Aposhian HV (1997). Enzymatic methylation of arsenic species and other new approaches to arsenic toxicity. *Annu Rev Pharmacol Toxicol* 37: 397-419.

Aposhian HV, Gurzau ES, Le XC, Gurzau A, Healy SM, Lu X, Ma M, Yip L, Zakharyan RA, Maiorino RM, Dart RC, Tircus MG, Gonzalez-Ramirez D, Morgan DL, Avram D and Aposhian MM (2000a). Occurrence of monomethylarsonous acid in urine of humans exposed to inorganic arsenic. *Chem Res Toxicol* 13(8): 693-7.

Aposhian HV, Zheng B, Aposhian MM, Le XC, Cebrian ME, Cullen W, Zakharyan RA, Ma M, Dart RC, Cheng Z, Andrewes P, Yip L, O'Malley GF, Maiorino RM, Van Voorhies W, Healy SM and Titcomb A (2000b). DMPS-arsenic challenge test. II. Modulation of arsenic species, including monomethylarsonous acid (MMA(III)), excreted in human urine. *Toxicol Appl Pharmacol* 165(1): 74-83.

Apostoli P, Alessio L, Romeo L, Buchet JP and Leone R (1997). Metabolism of arsenic after acute occupational arsine intoxication. *J Toxicol Environ Health* 52(4): 331-42.

Aranyi C, Bradof JN, Fenters JD, Graham JA and Miller FJ (1981). Effects of inhalation of arsenic trioxide aerosols in the pulmonary defenses of mice. In: *International Conference. Heavy Metals in the Environment. Commission of the European Communities and the World Health Organization.* 450-453.

Aranyi C, Bradof JN, O'Shea WJ, Graham JA and Miller FJ (1985). Effects of arsenic trioxide inhalation exposure on pulmonary antibacterial defenses in mice. *J Toxicol Environ Health* 15(1): 163-72.

ATSDR. (2000). *Arsenic. Toxicological Profile (Update)*. U.S. DHHS, Atlanta GA. <http://www.atsdr.cdc.gov/toxprofiles/fp2-c4.pdf>.

Baxley MN, Hood RD, Vedel GC, Harrison WP and Szczech GM (1981). Prenatal toxicity of orally administered sodium arsenite in mice. *Bull Environ Contam Toxicol* 26(6): 749-56.

Blair PC, Thompson MB, Bechtold M, Wilson RE, Moorman MP and Fowler BA (1990). Evidence for oxidative damage to red blood cells in mice induced by arsine gas. *Toxicology* 63(1): 25-34.

Blakley BR, Sisodia CS and Mukkur TK (1980). The effect of methylmercury, tetraethyl lead, and sodium arsenite on the humoral immune response in mice. *Toxicol Appl Pharmacol* 52(2): 245-54.

Blom S, Lagerkvist B and Linderholm H (1985). Arsenic exposure to smelter workers. Clinical and neurophysiological studies. *Scand J Work Environ Health* 11(4): 265-9.

Borgono JM, Vicent P, Venturino H and Infante A (1977). Arsenic in the drinking water of the city of Antofagasta: epidemiological and clinical study before and after the installation of a treatment plant. *Environ Health Perspect* 19: 103-5.

Brown MM, Rhyne BC and Goyer RA (1976). Intracellular effects of chronic arsenic administration on renal proximal tubule cells. *J Toxicol Environ Health* 1(3): 505-14.

Buchanan WD (1962). Arsine. In: *Toxicity of Arsenic Compounds*. Browning E. Elsevier. New York (NY): 67-75.

Buchet JP, Apostoli P and Lison D (1998). Arsenobetaine is not a major metabolite of arsine gas in the rat. *Arch Toxicol* 72(11): 706-10.

Buchet JP and Lauwerys R (1985). Study of inorganic arsenic methylation by rat liver in vitro: relevance for the interpretation of observations in man. *Arch Toxicol* 57(2): 125-9.

Buchet JP and Lauwerys R (1987). Study of factors influencing the in vivo methylation of inorganic arsenic in rats. *Toxicol Appl Pharmacol* 91(1): 65-74.

Buchet JP, Lauwerys R and Roels H (1981a). Comparison of the urinary excretion of arsenic metabolites after a single oral dose of sodium arsenite, monomethylarsonate, or dimethylarsinate in man. *Int Arch Occup Environ Health* 48(1): 71-9.

Buchet JP, Lauwerys R and Roels H (1981b). Urinary excretion of inorganic arsenic and its metabolites after repeated ingestion of sodium metaarsenite by volunteers. *Int Arch Occup Environ Health* 48(2): 111-8.

Calderon J, Navarro ME, Jimenez-Capdeville ME, Santos-Diaz MA, Golden A, Rodriguez-Leyva I, Borja-Aburto V and Diaz-Barriga F (2001). Exposure to arsenic and lead and neuropsychological development in Mexican children. *Environ Res* 85(2): 69-76.

Campbell D and Oates RK (1992). Childhood poisoning--a changing profile with scope for prevention. *Med J Aust* 156(4): 238-40.

Carter DE, Aposhian HV and Gandolfi AJ (2003). The metabolism of inorganic arsenic oxides, gallium arsenide, and arsine: a toxicochemical review. *Toxicol Appl Pharmacol* 193(3): 309-34.

Charbonneau SM, Spencer K, Bryce F and Sandi E (1978). Arsenic excretion by monkeys dosed with arsenic-containing fish or with inorganic arsenic. *Bull Environ Contam Toxicol* 20(4): 470-7.

Chen CJ, Chiou HY, Chiang MH, Lin LJ and Tai TY (1996). Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure. *Arterioscler Thromb Vasc Biol* 16(4): 504-10.

Chen CJ, Hsueh YM, Lai MS, Shyu MP, Chen SY, Wu MM, Kuo TL and Tai TY (1995). Increased prevalence of hypertension and long-term arsenic exposure. *Hypertension* 25(1): 53-60.

Chen CJ, Wu MM, Lee SS, Wang JD, Cheng SH and Wu HY (1988). Atherogenicity and carcinogenicity of high-arsenic artesian well water. Multiple risk factors and related malignant neoplasms of blackfoot disease. *Arteriosclerosis* 8(5): 452-60.

Chen KP and Wu HY (1962). Epidemiologic studies on blackfoot disease: II. A study of source of drinking water in relation to the disease. *J Formosan Med Assoc* 61: 611-618.

Chen Y, Factor-Litvak P, Howe GR, Graziano JH, Brant-Rauf P, Parvez F, Van Geen A, Ahsan H. (2006). Arsenic exposure from drinking water, dietary intakes of B vitamins and folate, and risk of high blood pressure in Bangladesh: A population-based, cross-sectional study. *Am J Epidemiol* 165:541-552.

Chi IC and Blackwell RQ (1968). A controlled retrospective study of blackfoot disease, an endemic peripheral gangrene disease in Taiwan. *Am J Epidemiol* 88: 7-24.

Chiou HY, Hsueh YM, Hsieh LL, Hsu LI, Hsu YH, Hsieh FI, Wei ML, Chen HC, Yang HT, Leu LC, Chu TH, Chen-Wu C, Yang MH and Chen CJ (1997a). Arsenic methylation capacity, body retention, and null genotypes of glutathione S-transferase M1 and T1 among current arsenic-exposed residents in Taiwan. *Mutat Res* 386(3): 197-207.

Chiou HY, Huang WI, Su CL, Chang SF, Hsu YH and Chen CJ (1997b). Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. *Stroke* 28(9): 1717-23.

Coles GA, Davies HJ, Daley D and Mallick NP (1969). Acute intravascular haemolysis and renal failure due to arsine poisoning. *Postgrad Med J* 45(521): 170-2.

Craig DK and Frye J. (1988). Acute LC50 nose only inhalation toxicity studies of arsine in rats (final report). N0512-4700. Batelle Columbus Labs. Columbus (OH)

Crump KS (1984). A new method for determining allowable daily intakes. *Fundam Appl Toxicol* 4(5): 854-71.

Crump KS and Howe R. (1983). Probit - A computer program to extrapolate quantile animal toxicological data to low doses. Crump K.S. & Company Inc.

Danielsson BR, Dencker L, Lindgren A and Tjalve H (1984). Accumulation of toxic metals in male reproduction organs. *Arch Toxicol Suppl* 7: 177-80.

DeSesso JM, Jacobson CF, Scialli AR, Farr CH and Holson JF (1998). An assessment of the developmental toxicity of inorganic arsenic. *Reprod Toxicol* 12(4): 385-433.

Engel RR and Smith AH (1994). Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States. *Arch Environ Health* 49(5): 418-27.

Ferm VH and Carpenter SJ (1968). Malformations induced by sodium arsenate. *J Reprod Fertil* 17(1): 199-201.

Flury F (1921). [Uber Kampfgasvergiftungen. IX. Lokal reizende Arsenverbindungen]. *Zeichschrift fur die Gesamte Experimentelle Medizin* 13: 527-528.

Flury F (1931). *Schadliche Gase - dampfe, nebel, rauch - und staubarten*. Berlin: Verlag von Julius Springer.

Fowler BA, Moorman MP, Adkins BJ, Bakewell WEJ, Blair PC and Thompson MB (1989). Arsine: toxicity data from acute and short-term inhalation exposures. In: ACGIH. *Hazard assessment and control technology in semiconductor manufacturing*. Lewis Publishers. Chelsea (MI): 85-89.

Frank G (1976). [Neurological and psychiatric disorders following acute arsine poisoning (author's transl)]. *J Neurol* 213(1): 59-70.

Freeman GB, Schoof RA, Ruby MV, Davis AO, Dill JA, Liao SC, Lapin CA and Bergstrom PD (1995). Bioavailability of arsenic in soil and house dust impacted by smelter activities following oral administration in cynomolgus monkeys. *Fundam Appl Toxicol* 28(2): 215-22.

Friberg L, Nordberg GF and Vouk VB, eds. (1986). *Handbook on the Toxicology of Metals*. Elsevier Amsterdam. p 59

Gates M, Williams J and Zapp JA. (1946). *Arsenicals. Summary technical report of Division 9, National Defense Research Committee. Vol. 1. Chemical warfare agents and related chemical problems.*: Office of Scientific Research and Development.

Gentry PR, Covington TR, Mann S, Shipp AM, Yager JW and Clewell HJ, 3rd (2004). Physiologically based pharmacokinetic modeling of arsenic in the mouse. *J Toxicol Environ Health A* 67(1): 43-71.

George B, Mathews V, Poonkuzhali B, Shaji RV, Srivastava A and Chandy M (2004). Treatment of children with newly diagnosed acute promyelocytic leukemia with arsenic trioxide: a single center experience. *Leukemia* 18(10): 1587-90.

Gladysheva TB, Oden KL and Rosen BP (1994). Properties of the arsenate reductase of plasmid R773. *Biochemistry* 33(23): 7288-93.

Grayson M, ed. (1978). Kirk-Othmer Encyclopedia of Chemical Technology. John Wiley and Sons New York. 247-251

Gregus Z, Gyurasics A and Csanaky I (2000). Biliary and urinary excretion of inorganic arsenic: monomethylarsonous acid as a major biliary metabolite in rats. *Toxicol Sci* 56(1): 18-25.

Grobe VJ (1976). [Peripheral circulatory disorders and acrocyanosis in arsenic exposed Moselle wine-growers]. *Berufsdermatosen* 24(3): 78-84.

Hafeman DM, Ahsan H, Louis ED, Siddique AB, Slavkovich V, Cheng Z, van Geen A and Graziano JH (2005). Association between arsenic exposure and a measure of subclinical sensory neuropathy in Bangladesh. *J Occup Environ Med* 47(8): 778-84.

Hammamoto E (1955). [Infant arsenic poisoning by powdered milk]. *Japanese Medical Journal* 1649: 2-12 [cited in ATSDR, 2006].

Harrison WP and Hood RD (1981). Prenatal effects following exposure of hamsters to sodium arsenite by oral or intraperitoneal routes [abstract]. *Teratology* 23: 40A [cited in Willhite and Ferm, 1984].

Hatlelid KM, Brailsford C and Carter DE (1995). An in vitro model for arsine toxicity using isolated red blood cells. *Fundam Appl Toxicol* 25(2): 302-6.

Hatlelid KM, Brailsford C and Carter DE (1996). Reactions of arsine with hemoglobin. *J Toxicol Environ Health* 47(2): 145-57.

Hayakawa T, Kobayashi Y, Cui X and Hirano S (2005). A new metabolic pathway of arsenite: arsenic-glutathione complexes are substrates for human arsenic methyltransferase Cyt19. *Arch Toxicol* 79(4): 183-91.

Healy SM, Casarez EA, Ayala-Fierro F and Aposhian H (1998). Enzymatic methylation of arsenic compounds. V. Arsenite methyltransferase activity in tissues of mice. *Toxicol Appl Pharmacol* 148(1): 65-70.

Heywood R and Sortwell RJ (1979). Arsenic intoxication in the rhesus monkey. *Toxicol Lett* 3: 137-144.

Hogue CJ, Buehler JW, Strauss LT and Smith JC (1987). Overview of the National Infant Mortality Surveillance (NIMS) project--design, methods, results. *Public Health Rep* 102(2): 126-38.

Holson JF, Stump DG, Ulrich CE and Farr CH (1999). Absence of prenatal developmental toxicity from inhaled arsenic trioxide in rats. *Toxicol Sci* 51(1): 87-97.

Hood RD and Harrison WP (1982). Effects of prenatal arsenite exposure in the hamster. *Bull Environ Contam Toxicol* 29(6): 671-8.

HSDB (1995). Hazardous Substances Data Bank. National Library of Medicine.  
<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>.

Hughes MF, Menache M and Thompson DJ (1994). Dose-dependent disposition of sodium arsenate in mice following acute oral exposure. *Fundam Appl Toxicol* 22(1): 80-9.

IARC. (2004). *Some Drinking -water Disinfectants and Contaminants, including Arsenic*. 84. International Agency for Research on Cancer, World Health Organization, Lyon, France.

ICRP (1994). Human Respiratory Tract Model for Radiological Protection. International Commission on Radiological Protection. Publication 66 Annals of the ICRP. Tarrytown (NY): Elsevier Science Inc. 24(1-3).

Ihrig MM, Shalat SL and Baynes C (1998). A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. *Epidemiology* 9(3): 290-4.

IRDC. (1985). Three acute inhalation toxicity studies of arsine on rats (final reports). 533-001, 533-002, 533-003. International Research and Development Corporation. Mattawan (MI)

Itoh T, Zhang YF, Murai S, Saito H, Nagahama H, Miyate H, Saito Y and Abe E (1990). The effect of arsenic trioxide on brain monoamine metabolism and locomotor activity of mice. *Toxicol Lett* 54(2-3): 345-53.

Jacobson-Kram D and Montalbano D (1985). The reproductive effects assessment group's report on the mutagenicity of inorganic arsenic. *Environ Mutagen* 7(5): 787-804.

Ji G and Silver S (1992). Reduction of arsenate to arsenite by the ArsC protein of the arsenic resistance operon of *Staphylococcus aureus* plasmid pI258. *Proc Natl Acad Sci U S A* 89(20): 9474-8.

Jiang G, Gong Z, Li XF, Cullen WR and Le XC (2003). Interaction of trivalent arsenicals with metallothionein. *Chem Res Toxicol* 16(7): 873-80.

Kamil'dzhanov AX (1982). Hygiene basis for the maximum permissible concentration of arsenic trioxide in the ambient air. *Gig Sanit* 2: 74-75.

Kamkin AB (1982). [Review of the maximum permissible concentration of arsenic trioxide in the atmosphere of populated places]. *Gig Sanit*(1): 6-9.

Kitchin KT (2001). Recent advances in arsenic carcinogenesis: modes of action, animal model systems, and methylated arsenic metabolites. *Toxicol Appl Pharmacol* 172(3): 249-61.

Kleinfeld MJ (1980). Arsine poisoning. *J Occup Med* 22(12): 820-1.

- Klimecki WT and Carter DE (1995). Arsine toxicity: chemical and mechanistic implications. *J Toxicol Environ Health* 46(4): 399-409.
- Krafft T and Macy JM (1998). Purification and characterization of the respiratory arsenate reductase of *Chrysiogenes arsenatis*. *Eur J Biochem* 255(3): 647-53.
- Kurttio P, Komulainen H, Hakala E, Kahelin H and Pekkanen J (1998). Urinary excretion of arsenic species after exposure to arsenic present in drinking water. *Arch Environ Contam Toxicol* 34(3): 297-305.
- Lagerkvist B, Linderholm H and Nordberg GF (1986). Vasospastic tendency and Raynaud's phenomenon in smelter workers exposed to arsenic. *Environ Res* 39(2): 465-74.
- Lai MS, Hsueh YM, Chen CJ, Shyu MP, Chen SY, Kuo TL, Wu MM and Tai TY (1994). Ingested inorganic arsenic and prevalence of diabetes mellitus. *Am J Epidemiol* 139(5): 484-92.
- Landrigan PJ, Costello RJ and Stringer WT (1982). Occupational exposure to arsine. An epidemiologic reappraisal of current standards. *Scand J Work Environ Health* 8(3): 169-77.
- Le XC, Lu X, Ma M, Cullen WR, Aposhian HV and Zheng B (2000a). Speciation of key arsenic metabolic intermediates in human urine. *Anal Chem* 72(21): 5172-7.
- Le XC, Ma M, Cullen WR, Aposhian HV, Lu X and Zheng B (2000b). Determination of monomethylarsonous acid, a key arsenic methylation intermediate, in human urine. *Environ Health Perspect* 108(11): 1015-8.
- Levin-Scherz JK, Patrick JD, Weber FH and Garabedian C, Jr. (1987). Acute arsenic ingestion. *Ann Emerg Med* 16(6): 702-4.
- Levy GA (1947). A study of arsine poisoning. *Quart J Exp Physiol* 34: 47-67.
- Lewis DR, Southwick JW, Ouellet-Hellstrom R, Rensch J and Calderon RL (1999). Drinking water arsenic in Utah: A cohort mortality study. *Environ Health Perspect* 107(5): 359-65.
- Lugo G, Cassady G and Palmisano P (1969). Acute maternal arsenic intoxication with neonatal death. *Am J Dis Child* 117(3): 328-30.
- Lundgren KD (1954). [Damage to respiratory organs in workers in a smelting plant] cited in U.S. EPA, 1984. *Nord Hyg Tidskr* 3-4: 66-82.
- Mann S, Droz PO and Vahter M (1994). A physiologically based pharmacokinetic model for four major arsenic species in mammals. In: *Arsenic Exposure and Health Effects. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters*

Chappell W. R., Abernathy C. O. and Cothorn C. R. Northwood. Middlesex, England: 16: 219-231.

Mann S, Droz PO and Vahter M (1996a). A physiologically based pharmacokinetic model for arsenic exposure. I. Development in hamsters and rabbits. *Toxicol Appl Pharmacol* 137(1): 8-22.

Mann S, Droz PO and Vahter M (1996b). A physiologically based pharmacokinetic model for arsenic exposure. II. Validation and application in humans. *Toxicol Appl Pharmacol* 140(2): 471-86.

Marafante E and Vahter M (1987). Solubility, retention, and metabolism of intratracheally and orally administered inorganic arsenic compounds in the hamster. *Environ Res* 42(1): 72-82.

Marnell LL, Garcia-Vargas GG, Chowdhury UK, Zakharyan RA, Walsh B, Avram MD, Kopplin MJ, Cebrian ME, Silbergeld EK and Aposhian HV (2003). Polymorphisms in the human monomethylarsonic acid (MMA V) reductase/hGSTO1 gene and changes in urinary arsenic profiles. *Chem Res Toxicol* 16(12): 1507-13.

Mazumder DNG, Haque R, Ghosh N, De BK, Santra A, Chakraborty D and Smith AH (1998). Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal, India. *Int J Epidemiol* 27(5): 871-7.

Menzel DB, Ross M, Oddo SV, Bergstrom PD, Greene H and Roth RN (1994). A physiologically based pharmacokinetic model for ingested arsenic. In: *Arsenic Exposure and Health Effects. Special Issue of Environmental Geochemistry and Health. Science and Technology Letters*. Chappell W. R., Abernathy C. O. and Cothorn C. R. Northwood Middlesex, England: 16: 209-218.

Meza MM, Yu L, Rodriguez YY, Guild M, Thompson D, Gandolfi AJ and Klimecki WT (2005). Developmentally restricted genetic determinants of human arsenic metabolism: association between urinary methylated arsenic and CYT19 polymorphisms in children. *Environ Health Perspect* 113(6): 775-81.

Morris JS, Schmid M, Newman S, Scheuer PJ and Sherlock S (1974). Arsenic and noncirrhotic portal hypertension. *Gastroenterology* 66(1): 86-94.

Morrissey RE, Fowler BA, Harris MW, Moorman MP, Jameson CW and Schwetz BA (1990). Arsine: absence of developmental toxicity in rats and mice. *Fundam Appl Toxicol* 15(2): 350-6.

Nagaraja TN and Desiraju T (1993). Regional alterations in the levels of brain biogenic amines, glutamate, GABA, and GAD activity due to chronic consumption of inorganic arsenic in developing and adult rats. *Bull Environ Contam Toxicol* 50(1): 100-7.



- Nagaraja TN and Desiraju T (1994). Effects on operant learning and brain acetylcholine esterase activity in rats following chronic inorganic arsenic intake. *Hum Exp Toxicol* 13(5): 353-6.
- Nagymajtenyi L, Selyes A and Berencsi G (1985). Chromosomal aberrations and fetotoxic effects of atmospheric arsenic exposure in mice. *J Appl Toxicol* 5(2): 61-3.
- Nemec MD, Holson JF, Farr CH and Hood RD (1998). Developmental toxicity assessment of arsenic acid in mice and rabbits. *Reprod Toxicol* 12(6): 647-58.
- Nordstrom S, Beckman L and Nordenson I (1979). Occupational and environmental risks in and around a smelter in northern Sweden. V. Spontaneous abortion among female employees and decreased birth weight in their offspring. *Hereditas* 90(2): 291-6.
- NRC. (1984). *Emergency and Continuous Exposure Limits for Selected Airborne Contaminants*. . 1. National Academy Press, Washington, DC.
- NRC. (2001). *Arsenic in Drinking Water 2001 Update*. National Academy Press, Washington, DC.
- OEHHA. (1999). *The Air Toxics Hot Spots Program Risk Assessment Guidelines. Part II: Technical Support Document for Describing Available Cancer Potency Factors*. Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.
- OEHHA. (2000). *The Air Toxics Hot Spots Program Risk Assessment Guidelines. Part IV: Technical Support Document for Exposure Assessment and Stochastic Analysis*. Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.  
[http://www.oehha.ca.gov/air/hot\\_spots/pdf/May2005Hotspots.pdf](http://www.oehha.ca.gov/air/hot_spots/pdf/May2005Hotspots.pdf).
- OEHHA. (2004). *Public Health Goals for Arsenic in Drinking Water*. Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.  
<http://www.oehha.ca.gov/water/phg/allphgs.html>.
- OEHHA. (2007). *The Air Toxics Hot Spots Program Risk Assessment Guidelines. Part V. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels (5-15-07, draft)*. Air Toxicology and Epidemiology Branch. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.
- Offergelt JA, Roels H, Buchet JP, Boeckx M and Lauwerys R (1992). Relation between airborne arsenic trioxide and urinary excretion of inorganic arsenic and its methylated metabolites. *Br J Ind Med* 49(6): 387-93.
- Owen BA (1990). Literature-derived absorption coefficients for 39 chemicals via oral and inhalation routes of exposure. *Regul Toxicol Pharmacol* 11(3): 237-52.

Parish GG, Glass R and Kimbrough R (1979). Acute arsine poisoning in two workers cleaning a clogged drain. *Arch Environ Health* 34(4): 224-7.

Perry K, Bowler RG, Bucknell HM, Druett HA and Scilling RSF (1948). Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. II. Clinical and environmental investigations. *Br J Ind Med* 5: 6-15.

Peterson DP (1990). Personal communication.

Peterson DP and Bhattacharyya MH (1985). Hematological responses to arsine exposure: quantitation of exposure response in mice. *Fundam Appl Toxicol* 5(3): 499-505.

Pomroy C, Charbonneau SM, McCullough RS and Tam GK (1980). Human retention studies with 74As. *Toxicol Appl Pharmacol* 53(3): 550-6.

Radabaugh TR and Aposhian HV (2000). Enzymatic reduction of arsenic compounds in mammalian systems: reduction of arsenate to arsenite by human liver arsenate reductase. *Chem Res Toxicol* 13(1): 26-30.

Rael LT, Ayala-Fierro F and Carter DE (2000). The effects of sulfur, thiol, and thiol inhibitor compounds on arsine-induced toxicity in the human erythrocyte membrane. *Toxicol Sci* 55(2): 468-77.

Rahman M and Axelson O (1995). Diabetes mellitus and arsenic exposure: a second look at case-control data from a Swedish copper smelter. *Occup Environ Med* 52(11): 773-4.

Rahman M, Tondel M, Ahmad SA and Axelson O (1998). Diabetes mellitus associated with arsenic exposure in Bangladesh. *Am J Epidemiol* 148(2): 198-203.

Rahman M, Tondel M, Ahmad SA, Chowdhury IA, Faruquee MH and Axelson O (1999). Hypertension and arsenic exposure in Bangladesh. *Hypertension* 33(1): 74-8.

Rahman M, Vahter M, Sohel N, Yunus M, Wahed MA, Streatfield PK, Ekstrom EC, Persson LA. (2006). Arsenic exposure and age- and sex-specific risk for skin lesions: A population-based case-referent study in Bangladesh. *Environ Health Perspect* 114:1847-1852.

Rahman MS, Hall LL and Hughes MF (1994). In vitro percutaneous absorption of sodium arsenate in B6C3F1 mice. *Toxicol in Vitro* 8(3): 441-448.

Rees DC and Hattis D (1994). Developing quantitative strategies for animal to human extrapolation. In: *Principles and Methods of Toxicology*. Hayes A. W. Raven Press. New York.

Rosenberg HG (1974). Systemic arterial disease and chronic arsenicism in infants. *Arch Pathol* 97(6): 360-5.

Rozenshtein IS (1970). [Sanitary toxicological assessment of low concentrations of arsenic trioxide in the atmosphere]. *Gig Sanit* 35: 16-21.

Saha KC (2003). Saha's grading of arsenicosis progression and treatment. In: *Arsenic Exposure and Health Effects V*. Chappell W. R., Abernathy C. O. and Thomas D. J. Elsevier. San Diego: 391.

Sampayo-Reyes A, Zakharyan RA, Healy SM and Aposhian HV (2000). Monomethylarsonic acid reductase and monomethylarsonous acid in hamster tissue. *Chem Res Toxicol* 13(11): 1181-6.

Sanger DE (1987). Unpublished study cited in Blair et al., 1990. Amherst, MA: University of Massachusetts School of Public Health.

Schroeder HA and Mitchener M (1971). Toxic effects of trace elements on the reproduction of mice and rats. *Arch Environ Health* 23(2): 102-6.

Siripitayakunkit U, Lue S and Choprapawon C (2001). Possible effects of arsenic on visual perception and visual-motor integration of children in Thailand. In: *Arsenic Exposure and Health Effects*. Chappell W. R., Abernathy C. O. and Calderon R. L. Elsevier Science.

Siripitayakunkit U, Visudhiphan P, Pradipasen M and Vorapongsathron T (1999). Association between chronic arsenic exposure and children's intelligence in Thailand. In: *Arsenic Exposure and Health Effects*. Chappell W. R., Abernathy C. O. and Calderon J. Elsevier Science.

Smith AH, Goycolea M, Haque R and Biggs ML (1998). Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. *Am J Epidemiol* 147(7): 660-9.

Stump DG, Holson JF, Fleeman TL, Nemec MD and Farr CH (1999). Comparative effects of single intraperitoneal or oral doses of sodium arsenate or arsenic trioxide during in utero development. *Teratology* 60(5): 283-91.

Styblo M, Delnomdedieu M and Thomas DJ (1996). Mono- and dimethylation of arsenic in rat liver cytosol in vitro. *Chem Biol Interact* 99(1-3): 147-64.

Styblo M, Yamauchi H and Thomas DJ (1995). Comparative in vitro methylation of trivalent and pentavalent arsenicals. *Toxicol Appl Pharmacol* 135(2): 172-8.

Tam GK, Charbonneau SM, Bryce F, Pomroy C and Sandi E (1979). Metabolism of inorganic arsenic (<sup>74</sup>As) in humans following oral ingestion. *Toxicol Appl Pharmacol* 50(2): 319-22.

Thomas R and Young R (2001). Arsine. Acute exposure guideline levels. *Inhal Toxicol* 13 (Suppl): 43-77.

Thompson DJ (1993). A chemical hypothesis for arsenic methylation in mammals. *Chem Biol Interact* 88(2-3): 89-14.

Tsai SY, Chou HY, The HW, Chen CM and Chen CJ (2003). The effects of chronic arsenic exposure from drinking water on the neurobehavioral development in adolescence. *Neurotoxicology* 24(4-5): 747-53.

Tseng CH, Chong CK, Chen CJ and Tai TY (1996). Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. *Atherosclerosis* 120(1-2): 125-33.

Tseng WP (1977). Effects and dose--response relationships of skin cancer and blackfoot disease with arsenic. *Environ Health Perspect* 19: 109-19.

U.S. EPA. (2002). *Notice of Receipt of Requests to Cancel Certain Chromated Copper Arsenate (CCA) Wood Preservative Products and Amend to Terminate Certain Uses of CCA Products* OPP-66300; FRL-6826-8. U.S. Environmental Protection Agency.

U.S. EPA. (2006a). *EPA Chemical Profiles: Arsine*. U. S. Environmental Protection Agency. <http://yosemite.epa.gov/oswer/ceppoehs.nsf/Profiles/1303-28-2?OpenDocument>.

U.S. EPA. (2006b). *Organic herbicides (MSMA, DSMA, CAMA, and Cacodylic Acid), Registration Eligibility Decision: Notice of Availability*. Volume 71, No 153. Federal Register: August 9, 2006.

Vahter M (1981). Biotransformation of trivalent and pentavalent inorganic arsenic in mice and rats. *Environ Res* 25(2): 286-93.

Vahter M (1983). Metabolism of arsenic. In: *Biological and Environmental Effects of Arsenic*. Fowler B. A. Elsevier. Amsterdam: 171-198.

Vahter M, Concha G, Nermell B, Nilsson R, Dulout F and Natarajan AT (1995a). A unique metabolism of inorganic arsenic in native Andean women. *Eur J Pharmacol* 293(4): 455-62.

Vahter M, Couch R, Nermell B and Nilsson R (1995b). Lack of methylation of inorganic arsenic in the chimpanzee. *Toxicol Appl Pharmacol* 133(2): 262-8.

Vahter M and Envall J (1983). In vivo reduction of arsenate in mice and rabbits. *Environ Res* 32(1): 14-24.

Vahter M, Friberg L, Rahnster B, Nygren A and Nolinder P (1986). Airborne arsenic and urinary excretion of metabolites of inorganic arsenic among smelter workers. *Int Arch Occup Environ Health* 57(2): 79-91.

Vahter M, Marafante E and Dencker L (1984). Tissue distribution and retention of <sup>74</sup>As-dimethylarsinic acid in mice and rats. *Arch Environ Contam Toxicol* 13(3): 259-64.

Vallee BL, Ulmer DD and Wacker WEC (1960). Arsenic toxicology and biochemistry. *Arch Ind Health* 21: 132-151.

von Ehrenstein OS, Guha Mazumder DN, Hira-Smith M, Ghosh N, Yuan Y, Windham G, Ghosh A, Haque R, Lahiri S, Kalman D, Das S and Smith AH (2006). Pregnancy outcomes, infant mortality, and arsenic in drinking water in West Bengal, India. *Am J Epidemiol* 163(7): 662-9.

von Ehrenstein OS, Mazumder DN, Yuan Y, Samanta S, Balmes J, Sil A, Ghosh N, Hira-Smith M, Haque R, Purushothamam R, Lahiri S, Das S and Smith AH (2005). Decrements in lung function related to arsenic in drinking water in West Bengal, India. *Am J Epidemiol* 162(6): 533-41.

Wagstaff DJ (1978). Alteration of hepatic detoxication enzyme activity by dietary arsenic trioxide. *Food Cosmet Toxicol* 16(5): 423-6.

Walton FS, Waters SB, Jolley SL, LeCluyse EL, Thomas DJ and Styblo M (2003). Selenium compounds modulate the activity of recombinant rat AsIII-methyltransferase and the methylation of arsenite by rat and human hepatocytes. *Chem Res Toxicol* 16(3): 261-5.

Wang CH, Jeng JS, Yip PK, Chen CL, Hsu LI, Hsueh YM, Chiou HY, Wu MM and Chen CJ (2002). Biological gradient between long-term arsenic exposure and carotid atherosclerosis. *Circulation* 105(15): 1804-9.

Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, van Geen A, Slavkovich V, Lolacono NJ, Cheng Z, Hussain I, Momotaj H and Graziano JH (2004). Water arsenic exposure and children's intellectual function in Araihaazar, Bangladesh. *Environ Health Perspect* 112(13): 1329-33.

Webb DR, Wilson SE and Carter DE (1986). Comparative pulmonary toxicity of gallium arsenide, gallium(III) oxide, or arsenic(III) oxide intratracheally instilled into rats. *Toxicol Appl Pharmacol* 82(3): 405-16.

Wester RC, Hui X, Barbadillo S, Maibach HI, Lowney YW, Schoof RA, Holm SE and Ruby MV (2004). In vivo percutaneous absorption of arsenic from water and CCA-treated wood residue. *Toxicol Sci* 79(2): 287-95.

Wester RC, Maibach HI, Sedik L, Melendres J and Wade M (1993). In vivo and in vitro percutaneous absorption and skin decontamination of arsenic from water and soil. *Fundam Appl Toxicol* 20(3): 336-40.

Wildfang E, Zakharyan RA and Aposhian HV (1998). Enzymatic methylation of arsenic compounds. VI. Characterization of hamster liver arsenite and methylarsonic acid methyltransferase activities in vitro. *Toxicol Appl Pharmacol* 152(2): 366-75.

Willhite CC and Ferm VH (1984). Prenatal and developmental toxicology of arsenicals. In: Nutritional and Toxicological Aspects of Food Safety. Friedman M. Plenum Publishing Corp. New York (NY): 9: 205-228.

Williams PL, Spain WH and Rubenstein M (1981). Suspected arsine poisoning during the restoration of a large cyclorama painting. *Am Ind Hyg Assoc J* 42(12): 911-3.

Winski SL and Carter DE (1995). Interactions of rat red blood cell sulfhydryls with arsenate and arsenite. *J Toxicol Environ Health* 46(3): 379-97.

Woods JS and Fowler BA (1978). Altered regulation of mammalian hepatic heme biosynthesis and urinary porphyrin excretion during prolonged exposure to sodium arsenate. *Toxicol Appl Pharmacol* 43(2): 361-71.

Wu MM, Kuo TL, Hwang YH and Chen CJ (1989). Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol* 130(6): 1123-32.

Yamauchi H and Yamamura Y (1985). Metabolism and excretion of orally administered arsenic trioxide in the hamster. *Toxicology* 34(2): 113-21.

Yu D (1999). A physiologically based pharmacokinetic model of inorganic arsenic. *Regul Toxicol Pharmacol* 29(2 Pt 1): 128-41.

Yu HS, Sheu HM, Ko SS, Chiang LC, Chien CH, Lin SM, Tserng BR and Chen CS (1984). Studies on blackfoot disease and chronic arsenism in southern Taiwan: with special reference to skin lesions and fluorescent substances. *J Dermatol* 11(4): 361-70.

Yu L, Kalla K, Guthrie E, Vidrine A and Klimecki WT (2003). Genetic variation in genes associated with arsenic metabolism: glutathione S-transferase omega 1-1 and purine nucleoside phosphorylase polymorphisms in European and indigenous Americans. *Environ Health Perspect* 111(11): 1421-7.

Zakharyan R, Wu Y, Bogdan GM and Aposhian HV (1995). Enzymatic methylation of arsenic compounds: assay, partial purification, and properties of arsenite methyltransferase and monomethylarsonic acid methyltransferase of rabbit liver. *Chem Res Toxicol* 8(8): 1029-38.

Zakharyan RA and Aposhian HV (1999). Enzymatic reduction of arsenic compounds in mammalian systems: the rate-limiting enzyme of rabbit liver arsenic biotransformation is MMA(V) reductase. *Chem Res Toxicol* 12(12): 1278-83.

Zakharyan RA, Sampayo-Reyes A, Healy SM, Tsaprailis G, Board PG, Liebler DC and Aposhian HV (2001). Human monomethylarsonic acid (MMA(V)) reductase is a member of the glutathione-S-transferase superfamily. *Chem Res Toxicol* 14(8): 1051-7.

Zakharyan RA, Wildfang E and Aposhian HV (1996). Enzymatic methylation of arsenic compounds. III. The marmoset and tamarin, but not the rhesus, monkeys are deficient in

methyltransferases that methylate inorganic arsenic. *Toxicol Appl Pharmacol* 140(1): 77-84.

Zaldivar R and Guillier A (1977). Environmental and clinical investigations on endemic chronic arsenic poisoning in infants and children. *Zentralbl Bakteriol [Orig B]* 165(2): 226-34.